Reminder on the Procoralan/Corlentor conditions of use for the symptomatic treatment of chronic stable angina pectoris to avoid potentially dangerous bradycardia, while clinical trial findings are being evaluated

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and the Maltese Medicines Authority, Les Laboratoires Servier would like to inform you of an emerging safety issue for Procoralan/Corlentor (ivabradine). Preliminary results of the SIGNIFY study have shown 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 indicate that the adverse cardiovascular outcomes may be mostly associated with the target heart rate being below 60 bpm; however data from the SIGNIFY study are being further evaluated to fully understand its implications for the clinical use of ivabradine.

In the interim, to avoid potentially dangerous bradycardia, health care professionals are reminded of the following:

Summary:

- **Initial data indicate that the adverse cardiovascular outcomes observed in the SIGNIFY study may be mostly associated with a target heart rate below 60 bpm. Treatment must be discontinued if resting heart rate becomes too low or symptoms of bradycardia persist.**

- **The usual recommended starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.**

- **If resting heart rate decreases persistently or the patient experiences symptoms related to bradycardia, the 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.**

- **Concomitant use of ivabradine with heart rate-reducing calcium channel blockers such as verapamil or diltiazem should be avoided.**

- **While on treatment with ivabradine patients should be carefully monitored for the occurrence of too low resting heart rates or symptoms of bradycardia. Treatment of patients currently using ivabradine should be reviewed where appropriate.**

In addition, health care professionals are reminded of the following:

- **Ivabradine is authorised for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm.**
- **Ivabradine is not a first-line treatment, but 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 and whose resting heart rate is > 60 bpm.**

<u>Further information on the preliminary findings from the SIGNIFY study:</u>

The SIGNIFY study was performed in patients with coronary artery disease without clinical heart failure. The posology used was higher than the posology recommended in the ivabradine SmPC (starting dose of 7.5 mg b.i.d. (5 mg b.i.d, if age > 75 years) and maintenance dose of up to 10 mg b.i.d).

In the randomized set (n=19102), ivabradine did not significantly affect the Primary composite Endpoint (PCE) (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%). Similar results were observed for cardiovascular deaths (hazard ratio 1.10, 95% CI [0.94–1.28], p=0.249, annual incidences of 1.49% vs. 1.36%) and non-fatal MI (hazard ratio 1.04, 95% CI [0.90–1.21], p=0·602, annual incidences of 1.63% vs. 1.56%). No excess of sudden deaths was observed suggesting no ventricular proarrhythmic effect of ivabradine.

In the pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12049), a statistically significant increase in the PCE was observed: 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 a non-statistically significant difference between treatment groups in the risk 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 MI (hazard ratio 1.18, 95% CI [0.97–1.42], p=0.092, annual incidences of 1.72% vs. 1.47%).

In this study, the incidence of bradycardia (symptomatic and asymptomatic) was high for ivabradine: 17.9 % vs. 2.1 % in the placebo group, with more than 30 % of the patients in the ivabradine group reaching at least once a resting HR below 50 bpm.
Initial analysis indicates that the adverse cardiovascular outcomes may be associated with the target heart rate (HR) being below 60 bpm; however study results are being further evaluated to fully understand its implications for the clinical use of ivabradine.

Ivabradine is also indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose resting heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.
Healthcare professionals should take note of the relevant precautions in the product information for this indication, especially in relation to heart rate.

Call for reporting

As a reminder, there is a need to report any suspected adverse reactions in accordance with the national spontaneous reporting system:
GALEPHARMA Ltd – Tel: +(356) 21 247 082 – 14-15, Strait Street, Valetta, VLT1430, Malta.

Alternatively any suspected adverse reactions can be reported to the Medicines Authority Post-licensing Directorate by filling in an ADR form and sending by post to 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA, or by email to postlicensing.medicinesauthority@gov.mt or submitting online at www.medicinesauthority.gov.mt/adrportal.

Company contact point

For further inquiries concerning this information, please contact GALEPHARMA Ltd
Tel: +(356) 21 247 082 – 14-15, Strait Street, Valetta, VLT1430, Malta.

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