
European Medicines Agency finalises review on Procoralan (ivabradine) and recommends measures to reduce the risk of heart problems.

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Information on Procorolan®

The European Medicines Agency (EMA) has completed a review of Procoralan (ivabradine) and has made recommendations aimed at reducing the risk of heart problems, including heart attack and bradycardia (excessively low heart rate), in patients taking the medicine for angina. Procoralan is used to treat symptoms of angina (chest pain due to problems with the blood flow to the heart) and to treat heart failure.

For more information please see Medicines Authority circular [P18/2014](#) on the start of the EMA's review.

Information from the European Medicines Agency

Procoralan has not been shown to provide benefits on reducing the risk of heart attack or cardiovascular death (death due to heart problems) therefore the medicine should only be used to alleviate symptoms of angina. Doctors should consider stopping treatment if there is no improvement in angina symptoms after 3 months, or if the improvement is only limited. When used for angina, Procoralan should only be started if the patient's resting heart rate is at least 70 beats per minute (bpm). Because

Other recommendations are that doctors must not prescribe Procoralan together with the medicines verapamil or diltiazem that reduce the heart rate, and that they should monitor their patients for atrial fibrillation (irregular rapid contractions of the upper chambers of the heart). If atrial fibrillation develops during treatment, the balance of benefits and risks of continued Procoralan treatment should be carefully reconsidered.

These recommendations are based on the EMA's review of the final data from the SIGNIFY study¹, which 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 heart attack with Procoralan compared with placebo (3.4% vs 2.9% yearly incidence rates). The data also indicated a higher risk of bradycardia with Procoralan compared with placebo (17.9% vs. 2.1%).

In its evaluation the EMA also assessed additional data on the safety and effectiveness of Procoralan which showed that the risk of atrial fibrillation is increased in patients treated with Procoralan compared with controls (4.9% vs 4.1%). In the SIGNIFY study, atrial fibrillation was observed in 5.3% of patients taking Procoralan compared with 3.8% in the placebo group.

Patients in the SIGNIFY study were started on a higher than recommended dose of Procoralan and received up to 10 mg twice a day, which is higher than the currently authorised maximum daily dose (7.5

mg twice a day). The EMA considered that the higher dose used in the study did not fully explain the findings. However, the Agency reiterated that the starting dose for angina should not exceed 5 mg twice a day and that the maximum dose should not exceed 7.5 mg twice a day.

The review of Procoralan was first carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations have now been endorsed by the Agency's Committee for Medicinal Products for Human Use (CHMP) in its final opinion. The CHMP opinion will be sent to the European Commission, which will issue a legally binding decision valid throughout the EU in due course.

For more information on Procoralan please read the European Public Assessment Report on the EMA's website www.ema.europa.eu

In Malta

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- The benefit-risk balance of Procoralan remains positive for its authorised indications. Because of a small but significant increase of the combined risk of cardiovascular death, myocardial infarction and heart failure seen in patients with symptomatic angina in the SIGNIFY study, recommendations have been issued to reduce this risk.
- The data from SIGNIFY did not demonstrate a beneficial effect for Procoralan on cardiovascular outcomes in coronary artery patients without clinical heart failure. Its use is only beneficial for symptomatic treatment in patients with chronic stable angina pectoris who cannot be treated with beta-blockers, or in combination with beta-blockers in case their disease is not controlled with them alone.
- In the symptomatic treatment of patients with chronic stable angina, Procoralan should only be started if the patient's resting heart rate is above or equal to 70 beats per minute (bpm).
- The starting dose of Procoralan should not exceed 5 mg twice daily and the maintenance dose of Procoralan should not exceed 7.5 mg twice daily.
- Procoralan should be discontinued if the symptoms of angina do not improve within 3 months. In addition, discontinuation should be considered if the improvement is only limited and if there is no clinically relevant reduction in resting heart rate within 3 months.
- The concomitant use of Procoralan with verapamil or diltiazem is now contraindicated.
- Prior to starting treatment or when considering titration, serial heart rate measurements, ECG, or ambulatory 24-hour monitoring should be considered when determining the heart rate.
- The risk of developing atrial fibrillation is increased in patients treated with Corlentor/Procoralan. Regular monitoring for the occurrence of atrial fibrillation is recommended. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued Procoralan treatment should be carefully reconsidered.
- If during treatment the heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be decreased (the lowest dose is 2.5 mg twice daily). If, despite dose reduction, the heart rate remains below 50 bpm or symptoms of bradycardia persist, treatment must be discontinued.
- Healthcare professionals should have been informed in writing of these new recommendations through a Direct Healthcare Professional Communication (DHPC) sent by Servier Malta in

beginning of December. A copy of this letter can be found on our website at www.medicinesauthority.gov.mt/dhpc

Information to patients

- Procortalan is a medicine used to treat symptoms of angina (chest pain due to problems with the blood flow to the heart) and to treat heart failure. Because patients treated with Procortalan for angina symptoms may be at increased risk of heart problems such as heart attack, recommendations have been issued to reduce this risk and ensure that the benefits continue to outweigh the risks.
- Your doctor will only start Procortalan if your resting heart rate is at least 70 beats per minute (bpm). Your doctor will regularly measure your heart rate particularly before starting treatment and when adjusting the dose.
- Your doctor will start treatment with Procortalan at a dose of up to 5 mg twice daily and increase it if necessary to a maximum of 7.5 mg twice daily.
- Your doctor will stop treatment with Procortalan if your symptoms of angina (such as shortness of breath) do not improve within 3 months or if the improvement is only limited.
- Procortalan must not be used together with the medicines verapamil or diltiazem which reduce the heart rate.
- As Procortalan could cause irregular rapid contractions of the upper chambers of the heart (a condition known as atrial fibrillation) your doctor will monitor your heart function regularly and will reconsider treatment if atrial fibrillation develops.
- If you have any questions or concerns, you should consult your doctor or another healthcare professional.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on ivabradine containing medicines. Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form or online at <http://www.medicinesauthority.gov.mt/adrportal> or to the marketing authorisation holder or their local representatives.

Prof. John J Borg PhD (Bristol)
Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicine Authority website for product safety updates as these are issued on an ongoing basis.