



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 January 2015
EMA/35715/2015

European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine)

On 20 November 2014, the European Medicines Agency (EMA) completed a review of Corlentor/Procoralan (ivabradine) and 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. Corlentor/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.

When used for angina, Corlentor/Procoralan should only be started if the patient's resting heart rate is at least 70 beats per minute (bpm). Because Corlentor/Procoralan has not been shown to provide benefits such as reducing the risk of heart attack or cardiovascular death (death due to heart problems), 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.

Other recommendations are that doctors must not prescribe Corlentor/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 Corlentor/Procoralan treatment should be carefully reconsidered.

These recommendations are based on the EMA's review¹ 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 Corlentor/Procoralan compared with placebo (3.4% vs 2.9% yearly incidence rates). The data also indicated a higher risk of bradycardia with Corlentor/Procoralan compared with placebo (17.9% vs. 2.1%).

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

¹ 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> (accessed 14/11/14).



was observed in 5.3% of patients taking Corlentor/Procoralan compared with 3.8% in the placebo group.

Patients in the SIGNIFY study were started on a higher than recommended dose of Corlentor/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 Corlentor/Procoralan was first carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations have been endorsed by the Agency's Committee for Medicinal Products for Human Use (CHMP).

The CHMP opinion was sent to the European Commission, which issued a legally binding decision valid throughout the EU on 15 January 2015.

Information to patients

- Corlentor/Procoralan 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 Corlentor/Procoralan 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 Corlentor/Procoralan 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 Corlentor/Procoralan 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 Corlentor/Procoralan if your symptoms of angina (such as shortness of breath) do not improve within 3 months or if the improvement is only limited.
- Corlentor/Procoralan must not be used together with the medicines verapamil or diltiazem which reduce the heart rate.
- As Corlentor/Procoralan 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.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- The benefit-risk balance of Corlentor/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 Corlentor/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, Corlentor/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 Corlentor/Procoralan should not exceed 5 mg twice daily and the maintenance dose of Corlentor/Procoralan should not exceed 7.5 mg twice daily.
- Corlentor/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 Corlentor/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 Corlentor/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 have been informed in writing of these new recommendations, and the product information for Corlentor/Procoralan has been updated accordingly.

More about the medicine

Corlentor and Procoralan are identical medicines that contain the active substance ivabradine. Corlentor/Procoralan is used to treat symptoms of long-term stable angina (chest pain due to problems with the blood flow to the heart) in adults with coronary heart disease (disease of the heart caused by the obstruction of the blood vessels that supply blood to the heart muscle) who have a normal heart rhythm. Corlentor/Procoralan is also used in patients with long-term heart failure (when the heart cannot pump enough blood to the rest of the body).

Corlentor/Procoralan is available as tablets. It works by lowering the heart rate thereby reducing the stress on the heart and slowing the progression of heart failure and reducing or preventing the symptoms of angina.

Corlentor/Procoralan received an EU-wide marketing authorisation on 25 October 2005.

More about the procedure

The review of Procoralan/Corlentor was initiated on 8 May 2014 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion.

The CHMP opinion was sent to the European Commission, which issued an EU-wide legally binding decision on 15 January 2015.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu