PROCORALAN®

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

PRESCRIBER GUIDE

(ivabradine hydrochloride)

Heart failure is a major problem for the health care systems all around the world, both in terms of cost but also of the impact on the patient's daily life. That is why it is essential that health care professionals join the efforts to fight this growing epidemic.

To optimize heart failure care, we are pleased to provide you with this prescriber guide containing useful information to help the doctor to prescribe Procoralan®.

The CHECK-LIST below should be filled in at each initiation with Procoralan® treatment.

Procoralan (Ivabradine) prescription checklist:
❍ **Stable, symptomatic Chronic Heart Failure (NYHA class II to IV)**
❍ **Systolic dysfunction (left ventricular ejection fraction ≤ 35%)**
❍ **Normal Sinus Rhythm**
❍ **Resting Heart Rate ≥ 70 bpm**
❍ **Patient is receiving standard therapies (ACEI, ARB, DIU, MRA if indicated)**
❍ **B-Blockers: at the Maximum tolerated dose or contraindicated**
❍ **Patient has been informed by his doctor about Procoralan® benefits and side effects**

This guide provides you with information and recommendations regarding appropriate and safe use of Procoralan® (ivabradine hydrochloride) in patients with chronic heart failure.

Therapeutic indication

Treatment of chronic heart failure

Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Recommended posology

Treatment initiation

The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure. The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

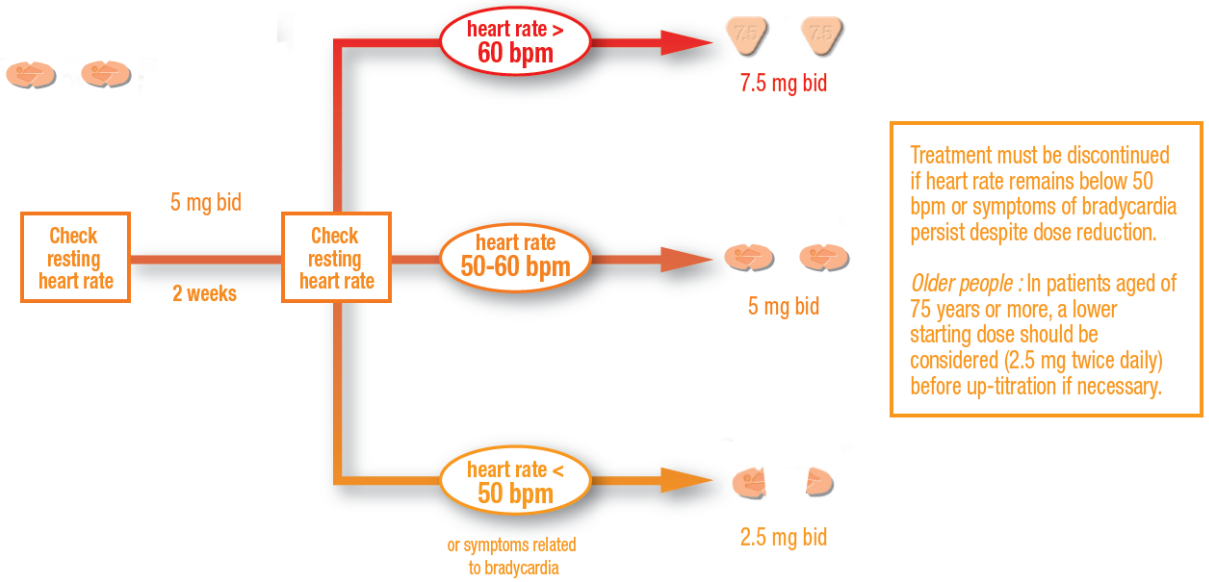
In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily *i.e.*one half 5 mg tablet twice daily) before up-titration if necessary.

During treatment period

If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist.

Dosage in heart failure patients



Procoralan® can be used in the following patients

- With stable chronic symptomatic heart failure NYHA II to IV class with systolic dysfunction (left ventricular ejection fraction ≤ 35%)
- On top of standard therapy including beta-blockers titrated to evidence based dose or at the maximum tolerated dose below the evidence based dose or when beta-blocker therapy is contraindicated or not well tolerated
- With resting heart rate above 70 bpm prior to treatment, after serial heart rate measurements, ECG or ambulatory 24-hour monitoring
- In sinus rhythm

Procoralan® is contraindicated and must not be used in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Resting heart rate below 70 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures

Monitoring of risk of bradycardia, atrial fibrillation and prolonged QT interval

Bradycardia

Bradycardia is a common adverse reaction (≥1/100 to <1/10) which is dose dependent and related to the pharmacological effect of ivabradine.

Therefore:

- Procoralan® should not be used in patients with resting heart rate <70 bpm prior to treatment.

- Procoralan® is contraindicated with strong cytochrome P450 3A4 inhibitors and with heart rate–reducing calcium channel blockers such as verapamil or diltiazem. The concomitant use of Procoralan® with other moderate cytochrome P450 3A4 inhibitors may be considered at the dose of 2.5 mg twice daily. The intake of grapefruit juice should be avoided during the treatment.

- Serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate before initiation of ivabradine treatment and when titration is considered.

- During treatment, if resting heart rate persistently falls below 50 bpm or if the patient experiences symptoms related to bradycardia, the dose must be titrated downward, or treatment discontinued if heart rate <50 bpm or symptoms persist.

Atrial fibrillation

Atrial fibrillation is a common adverse reaction (≥1/100 to <1/10) with ivabradine treatment.

Therefore:

- Procoralan® is not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.
- Procoralan®–treated patients should be regularly monitored for the occurrence of atrial fibrillation. Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur.
- If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

ECG prolonged QT interval

ECG prolonged QT interval is an uncommon adverse reaction (≥1/1000 to <1/100) with ivabradine treatment.

Therefore:

- The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided. If the combination appears necessary, close cardiac monitoring is needed.
  Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular *Torsade de pointes*.
- Potassium depleting diuretics (thiazide diuretics and loop diuretics) should be used with precaution in combination with ivabradine.

Side effects

The most common adverse reactions with Procoralan®, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

The other common adverse reactions with Procoralan® are headache, dizziness, blurred vision, AV 1st degree block (ECG prolonged PQ interval), ventricular extrasystoles, atrial fibrillation and uncontrolled blood pressure.

Counseling your patient

As part of discussions with your patients or their care givers, please ensure that:

- You provide a full description of the risks of bradycardia, atrial fibrillation and prolonged QT interval with Procoralan®
- You instruct the patient to read the Patient Information Leaflet
- You provide the patient with the Procoralan® Patient Guide

Please advise patient that, if symptoms of atrial fibrillation occur, they should seek medical advice immediately.

Further information on Procoralan®

For further information on Procoralan® please read the Summary of Product Characteristics here attached

Should you have any questions or need additional prescriber guide, our scientific information's department remains at your disposal.

Call for reporting
As a reminder, there is a need to report any suspected adverse reactions to the National Pharmacovigilance and Drug Safety Centre or Pharmacovigilance department in Servier, according to the following;

Saudi Food and Drug Authority Call Center: 19999
By e-mail: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa/

Pharmacovigilance department in Servier:
LPV: Ghaida AlAMMARI
E-mail: pv.sa1@servier.com
Tel.: +966 (0)11 25 22 330 Extn 304
Mobile: +966 (0)5 55 07 08 17

References

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2. Mostafa Q. Al-Shamiri. Heart Failure in the Middle East. Current Cardiology Reviews, 2013, 9, 174-178

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