

ivabradine: more precautions to protect patients with coronary artery disease because of its cardiac harms

● In 2015, the only action taken after the European review of *ivabradine* was the adoption of some restrictions on its use and some precautionary measures, despite the fact that this drug offers no advantages over other options and is known to have sometimes fatal cardiovascular adverse effects.

Ivabradine (Procoralan^o, Servier), an inhibitor of the cardiac IF current, offers no tangible advantages over alternative treatments in either angina or heart failure (1). Yet it can provoke adverse effects such as visual disturbances and sometimes fatal cardiovascular disorders, including severe bradycardia, atrial fibrillation (in about 5% of patients in clinical trials), prolongation of QT interval, torsades de pointes and myocardial infarction (1,2,3).

In mid-2014, a review by the European Pharmacovigilance Risk Assessment Committee (PRAC) was initiated in light of the preliminary results of a trial showing that *ivabradine* increased the combined risk of cardiovascular death and nonfatal myocardial infarction in patients

with symptomatic stable angina (3,4). In early 2015, the European Commission implemented the PRAC's recommendations: it revised the European Summaries of Product Characteristics (SPCs) of drugs containing *ivabradine*, in particular adding warnings about their use in patients with coronary artery disease (see below) (3,4,5).

In practice, *ivabradine* has more harms than benefits in both angina and heart failure. Since European health authorities have not yet decided to withdraw this drug from the market, it is advisable to simply avoid it. Other options better serve patients' interests: beta-blockers, *amlodipine* or *verapamil* in angina; while in heart failure, it is better to refrain from adding another drug to an optimised treatment regimen, or to use a beta-blocker with a proven impact on mortality (1).

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ivabradine

tablets

PROCORALAN^o

• 5 mg or 7.5 mg of *ivabradine* per tablet

inhibitor of the cardiac IF current

■ **Changes to the indications section** (text revised): "(...) *symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate greater than or equal to 70 bpm* [beats per minute] (...)

– in adults unable to tolerate or with a contraindication to the use of beta-blockers,
– or in combination with beta-blockers in patients inadequately controlled (...)" (1,2).

Prior to this revision, the minimum heart rate specified in the SPC for patients with angina was 60 bpm (2). The indication in heart failure has not been revised (1,2) EU centralised authorisation.

■ **Changes to the posology section** for chronic stable angina (text added): "*It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring (...). If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment (...) should be discontinued (...)*";

(text revised): "*The starting dose (...) should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic (...) and if resting heart rate remains above 60 bpm, the dose may be increased (...). The maintenance dose should not exceed 7.5 mg twice daily (...)*" (1,2).

Prior to this revision, the SPC did not specify a maximum dose for patients with angina (2).

■ **Changes to the special warnings section** (text added): "*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) (...)*" (1,2).

1- European Commission "Commission implementing decision (...) amending, under Article 20 of Regulation (EC) no 726/2004 (...) the marketing authorisation (...) for "Procoralan - Ivabradine" (...) + "Annexes" 15 January 2015: 65 pages.

2- European Commission "SPC-Procoralan" 22 August 2014: 31 pages.

Selected from Prescrire's literature search.

1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2015" *Prescrire Int* 2015; 24 (158): 78-79.

2- Prescrire Editorial Staff "Ivabradine and patients with coronary artery disease: more cardiovascular events" *Prescrire Int* 2014; 23 (155): 295.

3- European Commission "Commission implementing decision (...) amending, under Article 20 of Regulation (EC) no 726/2004 (...) the marketing authorisation (...) for "Procoralan - Ivabradine" (...) + "Annexes" 15 January 2015: 65 pages.

4- EMA - PRAC "Assessment report for ivabradine. Review under Article 20 of Regulation (...) " 6 November 2014: 15 pages.

5- ANSM "Point d'information - Procoralan (ivabradine): renforcement des précautions d'emploi pour minimiser le risque d'effets indésirables cardiovasculaires" 23 December 2014: 3 pages.