1 ABSTRACT

Title
Ivabradine Drug Utilisation Study in Select European Countries: A Multinational, Retrospective, Observational Study to Assess the Effectiveness of Risk-Minimisation Measures

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Keywords
Post-authorisation safety study (PASS), drug utilisation study (DUS), ivabradine hydrochloride, angina pectoris, risk-minimisation measures (RMM)

Rationale and background
Procoralan®/Corlentor® (ivabradine hydrochloride) received a marketing authorisation in Europe in 2005 for the symptomatic treatment of chronic stable angina pectoris in adult patients with normal sinus rhythm and a contraindication or intolerance for beta-blockers. In 2009, the indication was extended for use in combination with beta-blockers in patients with angina inadequately controlled with an optimal beta-blocker dose and heart rate > 60 bpm.
In May 2014, the European Commission triggered a benefit-risk re-evaluation of Procoralan/Corlentor following preliminary results from the SIGNIFY study. Following the Pharmacovigilance Risk Assessment Committee (PRAC) assessment, a direct healthcare professional communication (DHPC) was disseminated in European Union countries in December 2014 to inform on new RMM: an increase in the heart rate threshold (≥ 70 bpm) at initiation in patients with angina pectoris, a contraindication of verapamil and diltiazem, and to remind prescribers of dosing recommendations.

Research question and objectives
The overall objective of this DUS was to assess how ivabradine is used in patients with chronic stable angina pectoris in routine clinical practice and to evaluate the effectiveness of the new risk-minimisation measures. The study comprised two periods: before and after implementation of the risk-minimisation measures.
The specific objectives of the study were as follows:

- To describe the characteristics of new users of ivabradine before and after implementation of the risk-minimisation measures according to (1) demographics and specific comorbidities at baseline and (2) baseline heart rate at treatment initiation.
- To describe the patterns of use of ivabradine before and after implementation of the risk-minimisation measures according to (1) dose of ivabradine at treatment initiation and changes of dose within a 6-month follow-up period from treatment start and (2) concurrent use of verapamil or diltiazem at baseline and within a 6-month follow-up period.

Study design
Multinational, retrospective, observational, with 2 study periods according to RMM implementation:
- Before RMM: (01 January 2010 – 31 December 2013).
- After RMM: (30 June 2015 – 30 June 2016).

Setting
Patients' data at ivabradine initiation and during ≤ 6 months treatment collected through health care professionals in France, Germany, Italy, Spain, and the United Kingdom (UK).

Subjects and study size, including dropouts
Patients initiating treatment with ivabradine for chronic stable angina in routine clinical practice, 600 targeted per study period.

Variables and data sources
From patient medical records: age, sex, angina diagnosis, medical history, ivabradine prescription, specific comorbidities, heart rate at initiation, concomitant verapamil/diltiazem.

Results
A total of 60,675 sites were contacted over 6 waves of recruitment. The interest rate to participate in the study was low and ranged between 0.42% for general practitioners (GPs) in Italy and 1.87% for specialists in Italy.
A total of 80 sites participated, and 31 GPs and 37 specialists were active: 17 sites in France, 18 in Germany, 11 in Italy, 12 in Spain and 10 in the UK. A total of 1217 eligible patients were included in the study: 711 in the pre-RMM study period and 506 in the post-RMM study period. In both study periods, over 60% of patients were male, and over 65% of patients were aged < 75 years at ivabradine initiation. Compared to the pre-RMM period, in the post RMM period there were more patients with medical history of heart failure and hypertension, and less patients with medical history of sinus bradycardia. The percentage of patients who had undergone coronary angioplasty or bypass was similar in both periods.
The percentage of patients treated according to the current Summary of Product Characteristics (SmPC) (4 criteria, i.e., patients who were prescribed ivabradine according to the heart rate recommendation at baseline, no doses higher than the SmPC doses at treatment initiation and during follow-up, and had no concomitant use of verapamil or diltiazem at treatment initiation nor during follow-up) increased significantly in the post-RMM period (70.6% in the pre RMM study period and 78.4% in the post RMM study period; p value = 0.0035). This change in prescription patterns post RMM was observed in all the criteria assessed independently:
- The proportion of patients with heart rates ≥ 70 bpm at ivabradine treatment initiation increased in the post RMM study period compared to the pre-RMM study period (79.4% in the pre-RMM study period and 85.2% in the post RMM study period; p-value = 0.0141).
- The proportion of patients with no ivabradine dose higher than the SmPC doses at treatment initiation and during follow-up increased in the post-RMM study period compared to the pre-RMM study period (92.8% and 94.1% in the pre-RMM study period and post RMM study period, respectively, p-value = 0.3957). During follow-up in both study periods, 100% of patients with renewals data had ivabradine doses with respect to the SmPC doses regimen recommendations.

- The proportion of patients who had no concomitance with verapamil or diltiazem at ivabradine treatment initiation and during follow up increased in the post-RMM study period compared to the pre-RMM study period (96.1% and 99.2% in the pre-RMM and post-RMM study periods, respectively; p-value = 0.0007).

The change in prescription patterns in line with the current SmPC increased in the post-RMM study period compared to the pre-RMM study period 1) in both GPs and specialists and 2) in all countries except Italy. The overall decrease in Italy was driven by the decrease post-RMM in the adherence to heart rate threshold at initiation among cardiologists.
The sensitivity analysis taking into account patients with missing data in the denominator showed similar conclusions on adherence to RMM (65.5% in the pre-RMM study period and 72.3% in the post-RMM study period; p value = 0.0121).

Discussion
A significant change in prescription patterns in line with the current SmPC was observed overall (70.6% in the pre-RMM study period and 78.4% in the post-RMM study period) and in both specialists and GPs in all countries, except among Italian cardiologists. This could in part be explained by the shared care management, which was much more common in Italy than in the other countries, and which could have affected the quality of data reported at initiation.
The study aimed to ensure selection of a diverse and generally representative sample of physicians and their treated patients. However, having a total of 68 active sites across the 5 countries, only 1 GP in Italy and 2 specialists in the UK needs to be considered when interpreting the results. In addition, the comparison of results between countries requires consideration of the weight of shared-care management in each country and the difference in practice from one country to another for the same specialty.

In conclusion, the study results showed that the RMM were well implemented across the participating European countries. The prescription patterns have significantly changed to be in line with newly implemented RMM and the updated SmPC. Therefore, the benefit-risk balance of ivabradine in chronic stable angina pectoris remains favourable.

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