1 ABSTRACT

Title

Drug utilization study of mirabegron (Betmiga®) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland.

Keywords

Mirabegron, severe uncontrolled hypertension, risk minimisation, blood pressure monitoring, multicountry study, observational study, interrupted time series, Dear Healthcare Professional Communication.

Rationale and background

The mirabegron (Betmiga®) Summary of Product Characteristics (SmPC) states that the drug is contraindicated in patients with "Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg". In accordance and compliance with the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee's (PRAC's) request, a Direct Healthcare Professional Communication (DHPC) letter was disseminated on 7 September 2015 as a risk minimization activity. In line with the EMA CHMP guideline Module IX, an effectiveness check of this risk minimization activity was proposed by Astellas. A drug utilization study (DUS) on the use of mirabegron in the Netherlands, Spain, United Kingdom and Finland was performed as a risk minimization effectiveness check measure.

Research question and objectives

The objectives of the study were to assess the effectiveness of the DHPC letter as a risk minimization measure by quantifying the proportions of mirabegron initiators with documented hypertension (severe uncontrolled hypertension but also controlled hypertension or non-severe uncontrolled hypertension) (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment among hypertensive patients (secondary objective) before and after DHPC dissemination.

Study design

An observational retrospective cohort study among patients initiating mirabegron (Betmiga®) treatment using real-world data from the Netherlands, Spain, the United Kingdom and Finland was performed. The study compared the time periods relative to the DHPC letter dissemination.

Setting

Primary and secondary care as recorded in administrative healthcare databases reflecting usual care in the Netherlands, Spain, the United Kingdom and Finland.

Subjects and study size, including dropouts

Mirabegron initiators were identified in the period from first authorisation in December 2012 until December 2016 (end of data availability). At least 12 months of database history was

required which led to a total study population of 52,291 patients (3% excluded because of insufficient history): 7,762 from the Netherlands (3% excluded), 20,159 from Spain (<0.5% excluded), 17,980 (9% excluded) from the United Kingdom and 6,390 (3% excluded) from Finland.

Variables and data sources

Patient characteristics were assessed at the index date. Hypertension status at index date was assigned based on diagnoses of and treatment for hypertension and diastolic and systolic blood pressure (DBP and SBP) measurements. The frequency of blood pressure recordings was assessed prior to and during mirabegron treatment among initiators with hypertension at index date and compared with the frequency among initiators without hypertension.

The study was conducted utilizing the PHARMO Database Network (PHARMO) from The Netherlands, the Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària database (SIDIAP) from Catalonia (Spain), the Clinical Practice Research Datalink (CPRD) from the United Kingdom and the National registers and electronic medical record (EMR) data from Finland. These countries were chosen based on uptake of mirabegron and availability of linked prescription and blood pressure data.

Results

In all participating countries the proportions of mirabegron initiators with severe uncontrolled hypertension were low prior to DHPC dissemination (overall 145/29,799=0.49%). Observed proportions with severe uncontrolled hypertension after DHPC dissemination were also low (overall 124/21,062=0.59%). In the Netherlands, post-DHPC there was a lower proportion of patients with severe uncontrolled hypertension (0.61% pre-DHPC, 0.26% post-DHPC, p=0.053). In Spain and United Kingdom, pre-and post-DHPC proportions with severe uncontrolled hypertension were similar while in Finland there was a higher post-DHPC proportion of patients with severe uncontrolled hypertension (1.05% pre-DHPC, 1.60% post-DHPC, p=0.022). For non-severe uncontrolled hypertension, a lower proportion was observed post-DHPC in the Netherlands (15.84% pre-DHPC, 13.80% post-DHPC, p=0.038). In the Spanish database, a tendency toward a decrease in the proportion of patients with non-severe uncontrolled hypertension was observed after DHPC dissemination (12.54% pre-DHPC, 11.38% post-DHPC, (p=0.071). In the United Kingdom dataset, or in Finland except for the severe uncontrolled hypertension status, there was no association of DHPC dissemination and the proportion of mirabegron initiators with any hypertension status.

Blood pressure values at mirabegron initiation were available for 37% of patients pre-DHPC in the Netherlands, 55% in Spain, 56% in the United Kingdom and 29% in Finland and this changed little after DHPC dissemination. In all four countries a statistically significant yet marginal decrease in the median frequency of blood pressure recordings during mirabegron treatment was observed when periods before and after DHPC dissemination were compared.

Discussion

The use of mirabegron by patients with severe uncontrolled hypertension is uncommon, reflecting the low prevalence in the population but also suggesting that current labelling

seems to generally work well with respect to minimising risks in this population. No strong evidence of further risk reduction was observed in this study. In the Netherlands and possibly in Spain, slightly lower proportions of patients with severe uncontrolled hypertension were observed after DHPC dissemination. No risk minimisation was observed in the United Kingdom and a slight increase in the proportion of high-risk patients was observed in Finland. Considering the substantial variation between observations in all databases, these results should be interpreted with caution. No evidence of improved monitoring of blood pressure in hypertensive patients was observed.

Marketing Authorisation Holder(s)

Astellas Pharma Europe B.V.

Names and affiliations of principal investigators

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