TITLE

Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany

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Abstract

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Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany

Keywords

Flupirtine-containing medical products, drug utilisation, impact on risk minimisation measures.

Rationale and background

Due to a rising number of hepatotoxicity reactions during treatment with flupirtine-containing medical products the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) recommended in June 2013 to restrict the use of flupirtine-containing products. Flupirtine was restricted to treatment of acute pain for patients contraindicated for NSAIDs/weak opioids and duration of treatment not longer than 2 weeks. Furthermore, pre-existing liver disease or alcohol abuse are contraindications for flupirtine treatment and weekly liver function tests during treatment were recommended. In order to describe the drug utilisation before and after implementation of risk minimisation measures the Pharmacovigilance Risk Assessment Committee (PRAC) requested to implement a PASS as part of the Risk Management Plan (RMP).

Research question and objectives

Primary objectives:

Description of patients who have received flupirtine before and after implementation of risk minimisation measures. The following parameters were assessed:

- Estimate the proportion of patients with pre-existing liver disease or alcohol abuse problems
- Estimate the proportion of patients with pre-treatment with NSAIDs and weak opioids
- Estimate the proportion of patients with contraindications for NSAIDs and weak opioids
- Describe diagnoses related to the flupirtine prescription (indication)
- Evaluate the flupirtine treatment duration
- Estimate the proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Estimate the proportion of prescriptions with concomitant use of drugs known to have a potential hepatotoxic effect
- Estimate the proportion of prescriptions with liver function test (LFT) monitoring during flupirtine treatment

Secondary objective:

- Comparison of the length of treatment or proportions observed for each of the primary objectives in the patients initiating flupirtine after implementation of RMMs to treatment length or proportions observed in the patients treated with flupirtine before the implementation of risk minimisation measures (RMMs).

Study design

This study was implemented using two longitudinal patient level databases for Germany, one electronic medical records (EMR) database (IMS® Disease Analyzer) and one prescription database (IMS® LRx).

Setting

The study captured patients in the outpatient setting. All patients who have received at least one prescription for a flupirtine-containing product within the both defined 12-month period were included in the analysis.

Subjects and study size, including dropouts

All patients with a record of flupirtine prescription in the time periods April 2012 to March 2013 (reference period; before the Summary of Product Characteristics (SmPC) revision) or April 2015 to March 2016 (assessment period; after the SmPC revision) in the primary care physician (PCP) and orthopaedist panel of the IMS® Disease Analyzer and IMS® LRx database were considered for the study.

IMS® Disease Analyzer:

Reference period: 22,467 patients with 36,707 prescriptions

Assessment period: 14,703 patients with 21,167 prescriptions

IMS® LRx:

Reference period: 377,345 patients with 665,159 prescriptions

Assessment period: 164,669 patients with 258,752 prescriptions

Variables and data sources

PCP and orthopaedist panels of the IMS® Disease Analyzer:

Specialty, demographic data, co-morbidities, diseases leading to contraindications for NSAIDs and weak opioids, treatment with NSAIDs and weak opioids before flupirtine, indication for flupirtine prescription, treatment duration, single and repeated prescriptions and episodes, concomitant prescriptions of drugs known to have potential hepatotoxic effect, liver function tests.

IMS® LRx:

Specialty, demographic data, treatment with NSAIDs and weak opioids before flupirtine, treatment duration, single and repeated prescriptions and episodes, concomitant prescriptions of drugs known to have potential hepatotoxic effect.

Results

IMS® Disease Analyzer

In total, 22,467 patients with 36,707 prescriptions were available for the analysis of the reference period April 2012 to March 2013 and 14,703 patients with 21,167 prescriptions for the analysis of the assessment period April 2015 to March 2016. The majority of

patients in the reference period (19,088 of 22,467 patients) and in the assessment period (12,888 of 14,703 patients) were incident users.

Considering all co-morbidities documented in the entire available history, the percentage of patients with liver disease was 10.3% in the reference period and 10.7% in the assessment period. Alcohol dependence was recorded in both time periods for 1.5% of the patients. Within 12 months prior to the flupirtine prescription for 45.0% of patients in the reference period and 42.4% of patients in the assessment period any diagnosis of a disease contraindicated for NSAIDs or weak opioids were recorded. For half of the patients (reference period: 53.6%; assessment period: 51.5%) at least one prescription with NSAIDs or weak opioids was documented in the time period 12 month prior to the flupirtine prescription date.

For the majority of flupirtine prescriptions a diagnosis associated with acute pain was documented, either directly with the flupirtine prescription, within 2 weeks around the prescription date or within 12 months before prescription in both time periods (reference period: 72.3%; assessment period: 75.1%).

Short-term episodes (≤ 14 days) calculated based on Defined Daily Dose (DDD) were found for more patients in the assessment period than in the reference period. In the total group for 77.5% of patients only short-term episodes were recorded in the reference period and for 92.3% in the assessment period.

In the reference period 74.2% of the patients with follow-up of at least 3 months had a single flupirtine prescription. Single flupirtine prescriptions were more frequent in the assessment period with 82.6% in all patients.

At the same day prescriptions of drugs with known hepatotoxic effect was documented for 31.3% in the reference period and for 33.1% of flupirtine prescriptions in the assessment period.

In the reference period, for 7.3% of flupirtine prescriptions a LFT record within 1 week after prescription date was recorded. In the assessment period, a slightly higher value of 8.9% was observed.

IMS® LRx

In total, 377,345 patients with 665,159 prescriptions were available for the analysis of the reference period April 2012 to March 2013 and 164,669 patients with 258,752 prescriptions for the analysis of the assessment period April 2015 to March 2016. The majority of patients in the reference period (317,847 of 377,345) and in the assessment period (141,682 of 164,669) were incident users.

For more than half of the patients (reference period: 66.8%; assessment period: 65.7%) at least one prescription with NSAIDs or weak opioids was recorded in the 12 month history.

The length of episodes was evaluated based on DDD. In the reference period, only short-term episodes (≤ 14 days) were found in 71.1% of patients in the total group. In the assessment period, the percentage of patients with short-term episodes were larger than in the reference period with 91.8% in the total group.

In the reference period 69.6% of the patients with follow-up of at least 3 months had a single flupirtine prescription. Single flupirtine prescriptions were more frequent in the assessment period with 80.3% in all patients.

Prescriptions of drugs with known hepatotoxic effect was documented for 29.3% in the reference period and for 30.5% of flupirtine prescriptions in the assessment period.

Discussion

The findings of the PASS suggest that the implementation of RMM to restrict the prescription of flupirtine to patients with acute pain and for short term use has shown an effect.

The increase of patients with single flupirtine prescriptions and with treatment episodes less than 14 days indicate changes in the prescription behavior of physicians in Germany.

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