

Abstract

Title

Post-Authorisation Safety Study (PASS) on Flupirtine-containing Medicinal Products
A retrospective, multicentre, non-interventional study to evaluate the effectiveness of the risk minimisation activities for flupirtine-containing medicinal products

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Date of Abstract: 23 December 2016

Keywords

Post-Authorisation Safety Study (PASS), retrospective non-interventional observational study, flupirtine, effectiveness of the risk minimisation activities

Rationale and background

An increase in spontaneously reported hepatobiliary adverse drug reactions prompted a safety re-evaluation by the Pharmacovigilance Risk Assessment Committee (PRAC). It was concluded that the benefit-risk balance of flupirtine-containing medicinal products is favourable in the treatment of acute pain, subject to implementation of risk minimisation measures.

A Direct Healthcare Professional Communication (DHPC) was distributed in July 2013, SmPCs for flupirtine-containing medicinal products have been revised in September 2013 and the educational materials were distributed in February 2015.

Marketing authorisation holders (MAHs) distributed educational materials for flupirtine-containing medicinal products.

Research question and objectives

This post-authorization safety study (PASS) was designed to evaluate the effectiveness of the risk minimization measures (RMM) with regard to prescription behaviour of physicians representative for flupirtine prescribers in the therapy practice.

The following specific objectives were assessed:

Primary objective:

- Overall percentage of patients treated with flupirtine before and after implementation of the RMM for flupirtine determined as composite endpoint considering all following measures
 - Patients treated for acute pain
 - Patients treated up to a maximum of 14 days
 - Patients in whom other analgesics are contraindicated
 - Patients without pre-existing liver diseases classifiable according to SMQ hepatic disorders and without alcohol abuse
 - Patients not taking other medications known to cause drug induced liver injury (DILI)
 - Patients with weekly tests of liver function/liver enzymes during flupirtine treatment

Secondary objectives:

- Overall percentage of patients treated with flupirtine before and after implementation of the RMM for flupirtine
 - with abnormal liver function tests indicating a liver disease
 - in whom flupirtine treatment was discontinued due to abnormal liver function tests
 - experiencing hepatic adverse events classified according to SMQ hepatic disorders
- Frequency, nature and intensity of Adverse Events (AEs).

Study design

This PASS was performed according to Directive 2001/83/EC article 21a and 22a, Directive 2012/26/EU amending Directive 2001/83/EC as regards pharmacovigilance, Guideline on Good Pharmacovigilance Practice (GVP) Module V, VI, VIII and according to German Drug Law (Arzneimittelgesetz, AMG).

This PASS was designed as a retrospective, multicentre, non-interventional study in patients treated with flupirtine-containing medicinal products. The study design was discussed with the BfArM and approved.

Two observation periods were defined:

1. *Pre-intervention period: a defined six-month period before EMA referral of flupirtine*
01 April 2012 – 30 September 2012 (observation period 01)
2. *Post-intervention period: a defined six-month period after EMA regulatory action period*
01 April 2015 – 30 September 2015 (observation period 02)

Setting

Potential study centres were selected and contacted at random from an extensive physicians database. Physicians willing to participate were included with a distribution being qualitatively (specialities) and quantitatively (ratio of specialities) representative for flupirtine prescribers provided they used to prescribe flupirtine in the intended pre- and / or post intervention period. Participating physicians were asked to complete a CRF (Case Report Form,).

All reasonable efforts were made to avoid any bias concerning selection of participating physicians and documented patients.

Subjects and study size, including dropouts

Based on the prescription frequency of flupirtine of an average six patients per quarter and centre, prescription data from about 170 physicians/study centres were expected to be sufficient to complete 1,000 patients. These study centres were planned to be selected at random from the database and asked for participation. In order to obtain a representative participation of all relevant prescriber groups with prescription rates above 0.3 %, it was planned to include about 135 general practitioners/internists/medical practitioners (main prescriber group), 13 orthopaedists, 7 surgeons, 4 diabetologists, 3 neurologists, 2 each anaesthesiologists and neuropsychiatrists, as well as 1 each rheumatologists, cardiologist, gastroenterologist and gynecologist. In case that some of the contacted study centres do not prescribe flupirtine or reject participation, triple the number of needed study centres (about 510 centres) was intended to be prospectively selected at random from the database. This list was to be used for recruitment for both study periods.

Variables and data sources

- Demographic data, relevant medical history (including pre-existing liver disease classifiable according to SMQ hepatic disorders)
- Indication for and duration of treatment
- Contraindication for other analgesics, e.g. NSAIDs (Non-Steroidal Anti-Inflammatory Drug) or weak opioids
- Concomitant medication(s) including Over the Counter drugs (OTC) drugs
- Liver disease according to SMQ hepatic disorders during course of treatment
- Alcohol abuse
- Liver function tests, including dates, frequency and laboratory results
- Signs, symptoms and/or abnormal liver enzymes (exceeding 3 ULN (Upper Limit of Normal)) which indicate potential hepatobiliary disorders during and up to four weeks after end of flupirtine treatment
- Occurrence, frequency and nature of AEs in the course of flupirtine treatment
- Premature termination of flupirtine treatment and reasons for termination

Evaluation for primary objectives comprised the percentage of patients:

- treated for acute pain
- treated up to a maximum of 14 days
- for whom other analgesics (e.g. NSAIDs or weak opioids) are contraindicated
- without pre-existing liver diseases and without alcohol abuse
- not taking other medications known to cause drug induced liver injury (DILI)
- with weekly tests of liver function/liver enzymes during flupirtine treatment

Results

In total, 2205 patients were included, 1122 patients in the pre-intervention six-month period and 1083 patients in the post-intervention six-month period.

In total, 165 study centres participated in this study, for which quantitative speciality distribution was representative for flupirtine prescribers. (135 general practitioners/internists/medical practitioners, 12 orthopaedists, 5 surgeons, 4 diabetologists, 3 neurologists, 2 anaesthesiologists, as well as 1 neuro-psychiatrists each rheumatologists, cardiologist, and gastroenterologist. No gynaecologist participated although this was prospectively planned).

From every study centre, up to 12 patients treated with flupirtine were included.

The percentage of patients treated for the indication acute pain was quite high in both observation periods and increased further from 83.32 % in observation period 01 to 85.94 % (not statistically significant, p-value 0.0885).

The percentage of patients treated with flupirtine up to a maximum of 14 days increased significantly by more than 20 % (from 60.75 % in period 01 to 82.33 % in period 02; p-value < 0.0001).

The SmPC recommendation to treat patients with flupirtine only if treatment with other analgesics (e.g. NSAIDs, weak opioids) is contraindicated was followed for 60.21 % of the patients in period 01 and 55.78 % in period 02 (statistically significant, p-value 0.0351).

The revised SmPC required prescription of flupirtine only to patients without pre-existing liver diseases according to SMQ classification and without alcohol abuse. The percentage of patients for whom this requirement was followed, was very high in both periods with 94.56 % in period 01 and with 93.80 % in period 02. The small difference was statistically not significant (p-value 0.4482).

The percentage of patients who did not take any other medications known to cause DILI during the treatment with flupirtine increased by nearly 5 % from 69.40 % up to 73.82 % after implementation of the RMM (p-value 0.0216).

The overall percentage of patients, for whom the liver enzyme test was performed weekly, increased significantly from observation period 01 to 02 from 9.28 % to 12.03 % (p-value 0.0364).

Given the complexity of the primary objective that consisted of 6 endpoints only a small proportion of patients satisfied all risk minimization measures. Thus prior to introduction of the RMM, 2.68 % of patients fulfilled all sub-endpoints, after the introduction of the RMM, an increase up to 4.53 % was observed. This increase was statistically significant (p-value of 0.0192). However, the effectivity of the risk minimisation measurement is supported by the fact that the overall number of patients fulfilling at least 4 out of the 5 sub-endpoints increased significantly from 48.97% in period 1 to 62,72% (safety Set) in period 2. This increase was statistically highly significant with a p-value below 0.0001.

Amongst all AEs assessed, 9 hepatic AEs in each period were judged as possibly related to flupirtine treatment by the physicians (in period 02, for 1 patient 2 hepatic AEs were reported). For 7 patients in period 01 an increase of liver enzyme values > 3 x ULN during flupirtine treatment was reported, for 3 out of these 7 patients concomitant intake of medications causing DILI was reported. In period 02, 3 patients with increased liver enzymes were reported. More than half of these patients, presented single GGT elevations and included cases of alcohol dependence.

Discussion

The response rate of physicians contacted to the number finally participating was about 28,000 physicians contacted to 165 physicians finally participating. The voluntary participation of physicians is an inherent limitation of this study and may have favoured frequent prescribers with a strong flupirtine experience. However, because the ratio of specialities included reflects the known pattern of flupirtine prescribing physicians, the selection of sites is considered representative. Data were retrospectively collected from the physicians' medical records. Several measures were introduced into the study to avoid bias.

As RMM of PRAC, 6 new requirements for prescription of flupirtine have been introduced and the objective of this trial was to determine for how many patients under flupirtine the newly introduced prescription requirements were fulfilled before and after introduction of these new requirements.

Obviously, the strongest and statistically highly significant effect of the RMM was observed for the requirement to limit the duration of prescription to a maximum of 14 days reflected by an increase of more than 20 % (from 60.75 % in period 01 to 82.33 % in period 02; p-value < 0.0001). The limitation to the indication "acute pain" was already fulfilled for the majority of patients before introduction of the RMM (83.32 %) but still increased with statistical significance to 86.94 %. Also avoidance of concomitant intake of other medications known to cause DILI increased with statistical significance. Furthermore, the frequency of weekly liver enzyme testing increased from 9.16 % to 12.56 %, the increase was statistically significant. Obviously, flupirtine was already seldom prescribed to patients with pre-existing liver disease and alcohol abuse prior to introduction of RMM so that the ratio of patients fulfilling this prescription requirement remained on a high and stable level of nearly 95 %.

Only with regard to limiting, the prescription of flupirtine to those patients with existing contraindication for other analgesics the RMM showed no positive effect. However, in this study, the rationale behind the prescription decision could not be elucidated and there may have been a series of reasons why physicians decided to use flupirtine even if other analgesics were not contraindicated.

As requirement of BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte), the fulfillment of the combination of all 6 requirements was set as primary endpoint of this study. However, due to its complexity, this combined primary endpoint is obviously difficult to fulfil in therapeutic reality. Prior to introduction of the RMM, 2.68 % of patients fulfilled all sub-endpoints, i.e. the composite endpoint, after the introduction of the RMM, an increase up to 4.53 % was observed. But even this increase was statistically significant (p-value of 0.0192).

Overall, the PASS showed that the safety restrictions introduced following the referral procedure were fulfilled in small proportion of patients during the period before and after the referral, though there was a small but significant 2-fold increase in the physician's compliance toward the entire safety restrictions. Nonetheless, physicians are aware of and take into consideration the change in the SmPC in clinical practice, and restrict flupirtine prescriptions to the targeted patient population of acute pain as well as restrict prescription for short-term use (≤ 14 days). Also the proportion of patients who did not take any other medications known to cause DILI during the treatment with flupirtine increased significantly. Most restriction criteria were already met for large proportion of prescriptions in the pre-implementation period, except for weekly liver enzyme testing. Nonetheless, this proportion increased in the post-implementation period, indicating improve in compliance.