Abstract

Title

Retrospective Chart Review to Evaluate the Effectiveness of the Risk Minimization Measures for the Use of Flupirtine 100 mg Immediate-Release (IR) Capsules in Daily Practice (Study no.: Flupirtine-3300; version: 1; date: 09 December 2016; authors: [redacted]).

Keywords

Flupirtine, risk minimization measures, retrospective chart review (RCR)

Rationale and background

Flupirtine is a non-opioid, non-NSAID, non-steroidal analgesic, which has been authorised in the EU for the past 30 years. A review of available safety data from all manufacturers of flupirtine in 2013 revealed an increased number of hepatotoxic reactions. As a consequence to reduce the risk for hepatotoxic reactions the SmPC was updated, furthermore a "Dear Doctor letter" was sent out and educational material was implemented. In order to evaluate the effectiveness of these risk minimization activities for the use of flupirtine 100 mg IR capsules this RCR was performed as part of the risk management plan.

Research question and objectives

The overall research goal was to assess the effectiveness of the risk minimization measures for flupirtine 100 mg IR capsules by evaluating the compliance with the summary of product characteristics (SmPC, version Oct 2013) in daily practice.

Study design

This study was an international, multicentre, non-interventional post-authorization safety study (PASS) in the form of a RCR.

Setting

Information presented in this report was provided by outpatient care centres in Germany.

Subjects and study size, including dropouts

It was planned to include about 120 treating physicians with at least one flupirtine IR treated patient in at least one of the three specified 6-month time periods in 2012, 2014 or 2015. It was assumed that a minimum of 1200 prescriptions could be documented. No exclusion criteria were applied.

Variables and data sources

Physicians of the specialties of interest were recruited via internet portal, by emails and letters.

Main variables for analyses included number of prescribing physicians including setting and specialization, number and demographic characteristics of patients with flupirtine IR prescriptions, number of flupirtine IR prescriptions including information on indication, type of pain, prescribed product, pack size and posology, recommended and actual

treatment duration, reason(s) for end of therapy, concomitant diagnoses, concomitant medication with known potential of liver injury, results of liver function tests before and during treatment with flupirtine, hepatic AEs and non-hepatic ADRs.

Results Discussion

In total 588 prescriptions of flupirtine IR capsules of 429 patients were documented by 27 physicians in Germany within the three study periods. No data could be recorded in Portugal due to extensive regulatory requirements. Six individual non-compliance criteria related to the SmPC of 2013 were evaluated before (2012) and after referral (2014) as well as after referral and dissemination of further educational material (2015). SmPC compliance was given if none of the six non-compliance criteria was indicated.

The mean number of fulfilled non-compliance criteria was similar in the three study periods (3.0, 3.0 and 3.2 for 2012, 2014, and 2015, respectively). The most frequently fulfilled non-compliance criterion was “other analgesics not contraindicated” (92.3%, 93.5% and 94.6%) followed by “without sufficient number of liver function tests” (87.1%, 81.1% and 81.2%), “pre-existing liver disease, alcohol abuse and/or concomitant medication known to cause drug-induced liver injury” (47.2%, 56.8% and 48.9%), “treated for more than 14 days” (36.5%, 39.1% and 48.4%) and “not treated for acute pain / acute exacerbation of chronic pain” (32.6%, 33.1% and 46.8%). The proportion for “treatment not discontinued although abnormal liver function tests” was very low (0.4%, 1.2% and 1.6%).

Overall SmPC compliance was found for one prescription in any of the three study periods only. Thus outcome of this RCR might suggest that risk minimization measures were not effective. However, the number of participating physicians (in total N=27) as well as the number of documented prescriptions (in total N=588) were far too low to draw any meaningful conclusions and could not represent the prescription behaviour of the entity of flupirtine-prescribing physicians in Germany. The requirement of obtaining patients’ informed consent prior to start of documentation is considered as main reason for the low sample size (prescriptions and participating physicians). Methodological limitations including incomplete eCRF documentation might have led to an overestimation of non-compliance rates. When assessing the outcome of this RCR one should consider that 85% to 90% of prescriptions were single prescriptions only excluding a continuous use of the product over long treatment periods. Additionally, some parameters were not fully independent from each other (e.g. eCRF entries on “liver function tests” (documented on a very low level as could be expected based on the high number of single prescriptions) and “end of therapy in case of elevated liver enzymes”) and by that could not finally be judged.

Considering the general decrease in flupirtine prescriptions from 2012 to 2015 by 65% (Source: DUS Report [P2]) it could be concluded that physicians are aware of the restrictions regarding prescriptions of flupirtine IR capsules. But due to the fact of missing therapeutic alternatives (reason for prescription were: “alternative therapies were considered to be not sufficient” and/or “alternative therapies failed before” for ~2/3 of all prescriptions) a medical need for flupirtine IR capsules could be supposed. And by that, data of this RCR suggest that the prescribing physicians weighed up thoroughly the individual risk of a flupirtine IR treatment against patient’s individual benefit. Finally, taken all recorded information together it is concluded that the benefit-risk ratio for flupirtine IR capsules is unchanged positive.

As similar evaluations had to be done by the other MAHs of flupirtine-containing products it is expected that the full picture regarding SmPC compliance and effectiveness of risk minimization measures will only become apparent considering their data, too.

Thus it is further concluded that results of this RCR have no impact on the marketing authorisation of flupirtine IR capsules in general and on the effective SmPC in particular.

Marketing Authorisation Holder(s)

Germany: MEDA Pharma GmbH & Co. KG, Bad Homburg; TEVA GmbH, Ulm; Hormosan Pharma GmbH, Frankfurt; DR. KADE Pharmazeutische Fabrik GmbH, Berlin; Winthrop Arzneimittel GmbH, Frankfurt;
Portugal: MEDA Pharma - Produtos Farmacêuticos, S.A., Lisboa.

Names and affiliations of principal investigators

n/a