NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the Pharmacovigilance Risk Assessment Committee (PRAC) made by Germany – Federal Institute for Drugs and Medical Devices (BfArM):

Product Name	All Flupirtine-containing medicinal products
Active substance(s)	Flupirtine
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holder(s)	Various

Flupirtine is a 'selective neuronal potassium channel opener' (SNEPCO) that acts by reducing the excessive electrical activity that leads to many pain states. It also acts as functional N-methyl-D-aspartate (NMDA) receptor antagonist. Flupirtine is authorised in the European Union since 1984 as an alternative analgesic to opioids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the treatment of pain.

In March 2013, the European Medicines Agency (EMA) started a review under Article 107i of Directive 2001/83/EC for flupirtine-containing medicines notified by the Federal Institute for Drugs and Medical Devices (BfArM) following an increasing number of reports of drug-induced liver injury (DILI) ranging from asymptomatic increase in liver enzymes to liver failure, including a number of fatal cases and liver transplants (EMEA/H/A-107i/1363).

The referral concluded with the imposition of restrictions in the marketing authorizations for the medicinal products on the use of flupirtine limiting it to the treatment of acute (short-term) pain in adults only if treatment with other analgesics is contraindicated, and treatment lasting no longer than 2 weeks. In addition, patients' liver function testing was introduced after each full week of treatment to monitor any signs of liver problems and a contraindication was also implemented for patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause DILI.

Moreover, additional risk minimisation measures including the distribution of educational materials for physicians and patients and a Dear Health Care Professional Communication (DHPC) were implemented to communicate the risks and a post authorisation safety study (PASS) and a drug utilisation study (DUS) were imposed in order to characterise the prescribing patterns and evaluate the effectiveness of the above risk minimisation activities.

Three marketing authorisation holders (MAHs) or groups of MAHs have each submitted both a DUS and a PASS study report[1]. Despite different groups of participating physicians included in these studies, the results of the PASS are similar, showing a comparably very low degree of prescribers' adherence to the safety restrictions introduced after the 2013 referral procedure, and little improvement over time. Of note, in less than 5% of patients all

predefined criteria of compliance with the safety restrictions were fulfilled.

Importantly, the results of the DUS indicate a significant decrease in the number of patients and prescriptions over time, as well as an increase in the proportion of patients with a treatment duration ≤ 14 days. On the other hand, still up to one third of patients in 2015 showed a treatment duration >14 days with a mean treatment duration of up to 20.2 days.

Additionally, prescriptions given concomitantly with medication known to cause DILI were seen in up to 46.8% of the cases and prescriptions given concomitantly with NSAIDs or opioids medication were seen in 24.8% or 8.2% of the cases, respectively. Overall these incompliant prescriptions were still high at the end of the study periods and showed no relevant decrease over time. At the same time the proportions of patients with contraindications for other analgesics (as low as 39.3%) were low and showed no substantial increase. Furthermore very low rates ranging from 4.9% to 18.8% of patients or prescriptions with an adequate frequency of liver function tests were noted in all studies.

In conclusion, while the overall number of patients and prescriptions has decreased, those patients that are still prescribed flupirtine seem to be treated with a high degree of non-compliance with the safety restrictions introduced after the 2013 referral.

In addition, an analysis of both the individual case reports discussed by the MAHs and EudraVigilance data indicates that no reports resulting in a fatal outcome or liver transplantation were received after implementation of the RMMs in February 2015, but it remains unclear whether the absence of new reports with a fatal outcome or leading to liver transplantation is a direct effect of the implemented RMMs or merely caused by the substantial decrease in prescriptions observed since the last referral procedure. However, it is of concern that based on EudraVigilance data (23 February 2015 – 20 July 2017) cases of DILI, including serious reports and reports in patients without concomitant risk factors and/or a treatment duration ≤ 14 days continue to be received. In total 39 reports related to SOC "Hepatobiliary disorders", SMQ "Hepatic Disorders" or SMQ "Biliary disorders" were identified in the EudraVigilance database since implementation of the RMMs in 2015, including 37 serious reports and six reports of hepatic or liver failure. In four cases, including one case of hepatic failure, treatment duration was ≤ 14 days.

Further additional RMMs have been proposed by the MAHs (in addition to a DHPC), including a patient alert card to be distributed with the product package, a prescriber checklist, warnings on the outer package, changes to the product information and discontinuation of larger package sizes of 400 mg. It is however questionable whether these further measures could mitigate effectively the risk of hepatotoxicity in the light of the measures already implemented and the outcome of the PASS and DUS.

Therefore, in view of the recently available data of the non-adherence to the RMMs imposed as an outcome of the 2013 referral, and the cases of hepatic injury still being received, BfArM considers that the impact of the above concerns on the benefit-risk balance of the medicinal product need to be assessed at EU level.

In view of the above and the necessity to take action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.
As the request results from the evaluation of data resulting from pharmacovigilance activities, the position should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed

Date 19 October 2017

[redacted]

President of BfArM

[1] MEDA Pharma GmbH & Co. KG: PASS procedure EMEA/H/N/PSR/J/0007, national DUS procedure;
ratiopharm GmbH/TEVA GmbH group: national PASS and DUS procedure;
Hormosan Pharma GmbH and Aristo Pharma GmbH: national PASS and DUS procedure, identical study reports