# Annex II

# Scientific conclusions

## Scientific conclusions

In 2013, as a result of an urgent Union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1363), the marketing authorisations (MAs) for flupirtine-containing medicinal products were varied to impose restrictions and risk minimisations measures implemented in view of the risk of liver injury. In 2017, results of observational studies imposed as an outcome of this urgent union procedure indicated a low degree of compliance with the authorised terms of use of flupirtine-containing medicinal products and more specifically, with the above-mentioned restrictions and risk minimisations measures. In addition, cases of drug induced liver injury (DILI), including serious cases, continued to be received in EudraVigilance (EV) with flupirtine-containing medicinal products reported as suspected or interacting products.

In view of the recent study results and as cases of liver injury continue to be reported, the German national competent authority (BfArM) considered that the impact of the risk of liver injury on the benefit-risk balance of these medicinal products and the adequacy of the related risk minimisation measures, should be reviewed.

On 19 October 2017, the BfArM therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of flupirtine-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 8 February 2018 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

**Overall summary of the scientific evaluation by the PRAC**

Flupirtine is a ‘selective neuronal potassium channel opener’ that acts by opening Kv7 potassium channels leading to functional N-methyl-D-aspartate receptor antagonism. Additionally a facilitatory effect on gamma-aminobutyric acid A receptors has been described.

In 2013, an urgent union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1363) was initiated further to the increased reporting of hepatotoxicity reactions in association with flupirtine. Based on the review of all data available at the time, the PRAC concluded that flupirtine is associated with an increased risk of hepatotoxicity. At the time, the PRAC considered that the benefit-risk balance would remain favourable in the management of acute pain when treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated provided that a number of risk minimisation measures were implemented. These included the restriction of the maximum treatment duration to two weeks, a contraindication in patients with pre-existing liver disease or taking concomitantly other medication known to cause drug liver injury and weekly monitoring of liver functions. These measures were communicated to the relevant healthcare professional (HCP) in a letter and educational materials was implemented to inform prescribers and patients of the risk and associated measures to minimise it. The MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices and a post-authorisation safety study (PASS) to evaluate the effectiveness of the risk minimisation activities.

The PRAC considered all newly available safety and efficacy data, including information provided by the marketing authorisation holders on cases of liver injury, results of the above mentioned observational studies (DUS and PASS), data available in EudraVigilance and the scientific literature, in the context of the data reviewed in the previous Article 107i procedure.

The PRAC is of the opinion that the results of the newly available studies support the efficacy of flupirtine in the management of acute (nociceptive) pain (mild, moderate and severe) previously

demonstrated in clinical trials. It was noted that no medical guidelines recommending the use of flupirtine in any pain indication could be identified.

Data from spontaneous reports and the literature confirm the risk of unpredictable and potentially fatal liver injury associated to the use of flupirtine-containing medicinal products. Cases of drug induced liver injury (DILI), including cases of acute liver failure, cases necessitating a liver transplant and cases with a fatal outcome have been received since the previous review. Serious cases have also been received following the implementation of the related risk minimisation measures. PRAC considered that the newly available safety data, confirmed the known risk of unpredictable and potentially fatal liver injury.

Despite their limitations, the six observational studies conducted consistently showed a substantial lack of compliance with the measures required to minimise the risk of hepatotoxicity. Furthermore, the individual case reports of hepatobiliary toxicity show a substantial proportion of cases with non-compliance with the safety restrictions.

The PRAC concluded that while the use of flupirtine-containing products has decreased, the measures implemented have been ineffective to minimise the hepatotoxicity risk to an acceptable level.

The PRAC discussed whether further risk minimisation would sufficiently minimise the risk of hepatotoxicity. This included additional materials to communicate on the previous measures, reduction of the pack size, and introduction of a new warning regarding genetic risk factors. However, considering the failure of the previous measures, the absence of risk factors sensitive enough to predict the risk of hepatotoxicity, the clinical setting where these medicinal products are used, the PRAC could not identify further measures that would ensure effective minimisation of the risk of hepatotoxicity associated to the use of flupirtine-containing medicinal products. Therefore, in view of the impossibility to minimise sufficiently the risk of hepatotoxicity, the PRAC concluded that this risk outweighs the benefits of flupirtine in the treatment of acute pain, when treatment with other analgesics is contraindicated. Further, the PRAC could not identify conditions which if fulfilled in the future would demonstrate a positive benefit-risk balance for these products in their current indication. Consequently, the PRAC recommend the revocation of the marketing authorisations for flupirtine-containing medicinal products.

**Grounds for PRAC recommendation**

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for flupirtine-containing medicinal products (see Annex I).
- The PRAC reviewed all newly available safety and efficacy data, including information provided by the marketing authorisation holders on cases of liver injury, results of observational studies, data available in EudraVigilance and the scientific literature, in the context of the data reviewed in the previous procedure EMEA/H/A-107i/1363 and in relation to the risk of hepatotoxicity associated to flupirtine-containing medicinal products.
- The PRAC considered that there is no new significant information on the demonstrated efficacy of flupirtine in the management of acute (nociceptive) pain (mild, moderate and severe).
- The PRAC concluded that the safety data confirm that the use of flupirtine-containing medicinal products is associated with a risk of unpredictable and potentially fatal liver injury.
- Considering the new reports of liver injury, together with the results of observational studies, indicating a very low compliance to the measures recommended in 2013 to minimise the risk of

hepatotoxicity, the PRAC concluded that these measures have not been effective in adequately minimising the risk of hepatotoxicity.

- The PRAC discussed further risk minimisation proposals and concluded that no feasible measures would ensure effective minimisation of the hepatotoxicity risk to an acceptable level and that therefore this risk outweighs the benefits of flupirtine in the treatment of acute pain, when treatment with other analgesics is contraindicated.
- Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance for flupirtine-containing medicinal products in their current indication.

The Committee, as a consequence, considers that the benefit-risk balance of flupirtine-containing medicinal products is no longer favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for flupirtine-containing medicinal products.

**CMDh position**

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

***Overall conclusion***

The CMDh, as a consequence, considers that flupirtine-containing medicinal products are harmful. and their benefit-risk balance is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the revocation of the marketing authorisations for flupirtine-containing medicinal products.