NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 107i of Directive 2001/83/EC to the PRAC made by France:

Product Name(s) in the Referring Member State, if applicable	Fenspiride containing medicinal products.
Active substance(s)	Fenspiride
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s) in the referring Member State	LES LABORATOIRES SERVIER (SURESNES)

Background

Fenspiride is a systemic drug for obstructive airway diseases, thought to act through its antibronchoconstrictive and anti-inflammatory properties. These properties would result from the interaction of several interrelated mechanisms:

- Histamine H1 receptor antagonist activity and papaverinic (or musculotropic) type spasmolytic activity.
- Anti-inflammatory activity which would result from a reduction in the production of different pro-inflammatory factors, some of which also have bronchoconstrictive activity.

Fenspiride is indicated in the treatment of symptoms (cough and expectoration) related to bronchopulmonary diseases. Within the EEA, fenspiride-containing products are authorised in Bulgaria, France, Latvia, Lithuania, Poland, Portugal and Romania.

In the last PSUSA for fenspiride (PSUSA/00001368/201804) a cumulative review of QT prolongation/torsade de pointes identified four case reports of QT prolongation (including 3 with torsades de pointes) and two cases of sudden death. These cases were mainly reported with other confounding factors including concomitant administration of medicinal products known to prolong QT interval or other risk factor (e.g. overdose, dyskalemia, long QT syndrome). Nevertheless, due to close temporal relationship between the occurrence of the events and the onset of treatment with fenspiride, a potential effect of fenspiride on the QT interval could not be ruled out. A disproportionality analysis in the Eudravigilance database also identified a significant reporting odd ratio (ROR).

In order to further investigate this signal of QT prolongation, the MAH of the originator Pneumorel, Les Laboratoires SERVIER, committed to conduct a hERG channel binding study and to provide the final report to the relevant Competent Authorities by the end of January 2019.

Issues to be considered

The results of a standard *in vitro* model (hERG) assay, and an integrated *in vitro* study on isolated and perfused guinea pig hearts to investigate the potential of fenspiride to prolong ventricular repolarization with the ECG parameters measurement including QTc (Guinea-pigs isolated heart) were submitted to ANSM by the MAH Les Laboratoires SERVIER through a work-sharing type II variation procedure (FR/H/xxxx/WS/0139) on 30 January 2019. These results show that fenspiride at concentration levels of 10 and 30 µM induced an inhibition of hERG tail current, which results, at the same concentrations, in an increase in QTc intervals in isolated and perfused guinea pig heart.

Based on the hERG IC50 value observed in the *in vitro* hERG assay (=15.14µM), the calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration ranges from 6 for repeated administration (80mg b.i.d.) to 26 for single administration, which are lower than the lowest acceptable safety margin of 30 for drugs in the absence of interaction with other cardiac ion channels.

It should be noted that according to the SmPCs of the originator product Pneumorel, the maximum recommended dose could extend to 80mg t.i.d. and therefore the safety margin calculated above for repeated administration could be overestimated.

Based on these non-clinical results, it is likely that the conduct of a clinical ICH E14 study in humans would provide similar conclusions. In addition, a fifth case of QT prolongation was reported after the Data Lock Point (DLP) of the last PSUSA. Therefore, both the ANSM and the MAH considered that these new non-clinical findings, together with the accumulated post-marketing experience, support the risk of prolongation of the QTc interval in humans using fenspiride-containing medicinal products. In light of the above, the MAH considered that the benefit-risk ratio of this product is no longer considered favourable and indicated their intention to withdraw their worldwide marketing authorisations of Pneumorel.

In light of these new safety findings, taking into account that fenspiride is indicated as a symptomatic treatment and the seriousness of the risk of QT prolongation, the ANSM concluded that the benefit-risk ratio of fenspiride-containing medicinal products is no longer considered favourable in their authorised indications(s). On 8 February 2019, the ANSM has suspended the marketing authorizations of Pneumorel in France.

In view of the above, France initiates an urgent Union procedure under Article 107i of Directive 2001/83/EC and refers the matter to the PRAC which is requested to give its recommendation 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 opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed

Date 08 FEV. 2019

D[redacted]IER-CARBONNEIL

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