Annex II

Scientific conclusions

Scientific conclusions

Newly available results of two non-clinical studies showed that fenspiride can induce an inhibition of hERG tail current *in vitro*, and increase the corrected QT (QTc) intervals in isolated and perfused guinea pig heart. Calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration were below the lowest acceptable margin proposed in the literature for administration in humans. The French Competent Authority (ANSM) considered that these results taken together with pharmacovigilance data support the risk of prolongation of the QTc interval in these patients. Taking into account that fenspiride is indicated to treat benign symptoms and the seriousness of the risk of unpredictable QT prolongation leading to proarrhythmic potential in human, the ANSM concluded that the benefit-risk balance of fenspiride-containing medicinal products was no longer favourable in the treatment of symptoms related to bronchopulmonary diseases, and suspended the marketing authorisations of these products.

On 8 February 2019 the French Competent Authority (ANSM) therefore triggered an urgent Union procedure under Article 107i 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 fenspiride 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 16 May 2019 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

Fenspiride-containing medicinal products are authorised nationally for the treatment of symptoms (e.g. cough and expectoration) related to bronchopulmonary diseases.

The PRAC considered all data submitted by the MAHs, received from stakeholders and provided by EMA. This included the results of the above-mentioned requested non-clinical study (Aptuit), two other non-clinical studies and post-marketing case-reports as well as published efficacy studies.

Fenspiride has been shown in the Aptuit study to block hERG channels at supratherapeutic doses *in vitro* in a heterologous expression system, with an IC_{50} value of 15.14 µM. There is a possibility that the IC_{50} value is overestimated (i.e. experiments performed at room temperature, external K+ concentration in the milieu unknown, no DMSO cells perfusion before adding fenspiride in DMSO yet substracting DMSO effect) and fenspiride could be a more potent blocker of hERG channels than shown *in vitro*. The calculated safety margins between the hERG IC_{50} obtained and the effective therapeutic plasma concentration for fenspiride, was below the lowest acceptable safety margin proposed in the literature (between 6 and 26, depending on the pharmaceutical form/dose administered and on the administration schedule). These very low margins may have also been overestimated (i.e. plasma concentrations corresponding to the maximum daily doses were not determined, not clear whether the analysis was performed at steady state plasma concentrations or not). In addition, no protective effects regarding the triggering of TdP arrhythmias (blockade of Nav1.5 and cardiac L-type Ca2+ channels) was shown for fenspiride.

It has also been shown in a recent *ex vivo* study on isolated guinea pig hearts that the hERG blockade exerted by fenspiride may translate into QT prolongation in a similar concentration range as observed in the hERG study. The observed prolongation may be underestimated in this study due to the necessary QT correction formula of the observed dose-dependent QTc augmentations, in view of the method used. In addition, no effect of fenspiride was observed on the PR or QRS complex of the ECG, suggesting that fenspiride has no significant effect on other cardiac channels and no compensatory action of hERG blockade *in vivo*. QT/QTc interval prolongation was not accompanied by any events of arrhythmia or contracture on the guinea pig heart model at any assay concentration.

In *in silico* models, fenspiride induced QT prolongation and “early afterdepolarizations” (EADs; arrhythmic makers) in specific cardiovascular disease state models.

Regarding clinical data, analysis of post-marketing cases reported since the marketing authorisation showed evidence to support a causal association between occurrence of QT prolongation/TdP in patients, mostly with risk factors for these events, and the treatment with fenspiride-containing medicinal products. Additionally, unspecific terms of syncope, loss of consciousness, tachycardia and palpitations that may (among others) be signs and symptoms of TdP were present in a significant number of cases. It is noted that lack of ECG diagnosis is common in these cases, which generates significant uncertainty on the actual incidence of TdP.

In summary based on non-clinical assays of the accepted surrogate markers of TdP, i.e. blockade of hERG tail current and prolongation of the QT/QTc interval, and on post-marketing spontaneous reports of confirmed cases of TdP, QT prolongation and ventricular fibrillation/arrhythmia, the risk of QT prolongation, a proarrhythmic potential and associated risk of TdP is considered confirmed with fenspiride use.

Considering the seriousness of TdP which can lead to fatal outcome, a thorough risk analysis would be essential for each individual patient prior to treatment initiation with fenspiride. However, some risk factors of TdP like congenital long QT syndrome are usually silent and unpredictable. In addition, performing ECG or measurements of potassium or magnesium levels is neither considered proportionate in pre-treatment screening for a medicinal product solely used to treat benign symptoms of generally self-limiting conditions, nor feasible in clinical practice. The PRAC further noted that in view of the low safety margin calculated at doses below the therapeutic effect dose, reducing the dose would not permit to reduce the risk to an acceptable level.

In conclusion, no feasible and effective measures could be identified which would minimise this risk to an acceptable level. Therefore, the PRAC concluded that the risk of QT prolongation, the proarrhythmic potential and associated risk of TdP outweighs the benefits of fenspiride in its authorised indication(s). The PRAC noted that this conclusion was also reached by the MAH of the originator.

The PRAC considered that in view of the available data the generation of additional evidence via an ICH E14 thorough QT/QTc clinical study would not be justified and would not allow identifying defined patient population in whom the benefits could outweigh the risks.

Further, the PRAC could not identify condition(s) which if fulfilled would demonstrate a positive benefit-risk balance for these products in a defined patient population. Consequently, the PRAC recommended the revocation of the marketing authorisations for fenspiride-containing medicinal products.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for fenspiride-containing medicinal products (see Annex I).
- The PRAC reviewed the totality of the data available for fenspiride-containing medicinal products in relation to the risk of QT prolongation. This included the results of non-clinical studies and post-marketing case reports as well as published efficacy studies submitted by the MAHs, by stakeholders and provided by EMA.
- The PRAC considered that the use of fenspiride is associated with a risk of QT prolongation, and therefore it has proarrhythmic potential and present a risk of Torsade de Pointes (TdP). QT prolongation and TdP are unpredictable and potentially life-threatening conditions that

constitute a major safety concern, particularly given the benign symptoms for which fenspiride-containing medicinal products are used to treat.

- Taking into account that these medicinal products are only used to treat benign symptoms, the PRAC considered that no feasible and proportionate measures would effectively allow identifying patients with risk factors for QT prolongation and TdP, and that therefore any related risk minimisation measures could not be implemented in clinical practice. No other appropriate measure was identified that would reduce the risk of QT prolongation to an acceptable level.
- Further, the PRAC could not identify condition(s) to the marketing authorisation which if fulfilled would demonstrate a positive benefit-risk balance for these products in a defined patient population.

The Committee, as a consequence, considers that the benefit-risk balance of fenspiride-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 fenspiride-containing medicinal products.

CMDh position

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

The CMDh considered the arguments presented in writing by one MAH (Aflofarm Farmacja Polska Sp. Z O.O.) and concluded that all relevant elements had already been considered by PRAC. Therefore, the conclusions of the PRAC are not affected.

The CMDh, as a consequence, considers that the benefit-risk balance of fenspiride-containing medicinal products is not favourable. Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the revocation of the marketing authorisations for fenspiride-containing medicinal products.