16 May 2019
EMA/317731/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 107i of Directive 2001/83/EC

Fenspiride-containing medicinal products

INN/active substance: fenspiride

Procedure number: EMEA/H/A-107i/1480

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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 and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Fenspiride is authorised in European Union Member States (EU MSs) as a systemic medicinal product 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.
- Reduction in the production of different pro-inflammatory factors, some of which also have bronchoconstrictive activity.

Within the European Economic Area (EEA), fenspiride-containing products are authorised in Bulgaria, France, Latvia, Lithuania, Poland, Portugal and Romania, for the treatment of symptoms (e.g. cough and expectoration) related to bronchopulmonary diseases, with some differences in the exact indications in the MSs. They are available both as over the counter (OTC) and “prescription only” products. Fenspiride-containing products are authorised for oral use and are available in different types of tablets of 80 mg (prolonged-release, film-coated, coated, gastro-resistant), syrup of 0.2% (2 mg/ml) and oral drops solution of 25 mg/ml. The syrup formulation is indicated from the age of 2 years, whereas tablets are for adults only. The daily dose generally required for the tablets is 160 mg to 240 mg in adults and for the syrup 90 mg to 180 mg for adults and 4 mg/kg for children. The cumulative patient exposure is estimated at over 6 million patient-years.

In November 2018, in order to further investigate a signal of QT prolongation, the MAH of the originator medicinal product Pneumorel was requested to conduct a hERG channel binding study and to provide the final report to the relevant Competent Authorities by the end of January 2019, together with a discussion on the impact of these results on the benefit-risk balance and on whether a clinical study in line with the international conference on harmonisation (ICH) E14 guideline would be required (PSUSA/00001368/201804). The MAH conducted 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 electrocardiogram (ECG) parameters measurement including QTc (Guinea-pigs isolated heart) and submitted the results in a work-sharing type II variation procedure (FR/H/xxxx/WS/0139) on 30 January 2019. These non-clinical results 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. In addition, calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration were below the acceptable margin. Both the ANSM and the MAH considered that it is likely that a clinical study in humans would provide similar conclusions and 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 balance of this product was no longer favourable and indicated their intention to withdraw the marketing authorisations of Pneumorel worldwide.

In light of these new safety findings, taking into account that fenspiride is a symptomatic treatment of generally benign conditions (cough and expectoration) and the seriousness of the risk of QT prolongation, 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. On 8 February 2019, the ANSM suspended the marketing authorisations of Pneumorel in France and initiated an urgent Union procedure under Article 107i of Directive 2001/83/EC, referring the matter to the PRAC which was requested to give its recommendation as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

In February 2019 whilst the potential impact of these findings on the benefit-risk balance of fenspiride-containing products was being further reviewed, based on the information available to the Committee on the risk of QT prolongation and proarrhythmic potential, the PRAC recommended measures in order to protect patients [1]. Considering that QT prolongation and proarrhythmic potential are life-threatening and unpredictable conditions, and taking into account that the medicinal product is solely used to treat benign symptoms, the PRAC concluded that the only appropriate risk minimisation measure to protect patients was the suspension of the marketing authorisations. The PRAC considered then that the risk of QT prolongation and proarrhythmic potential outweighed the benefits of fenspiride in its authorised indications based on the available data at the time and recommended the suspension of the marketing authorisation for these products while the review was ongoing. This recommendation was sent to the EEA countries together with the agreed wording of a DHPC for dissemination. The present report relates to the complete review of this issue.

The PRAC considered all data submitted by the MAHs, received from stakeholders and provided by the EMA. This included the results of non-clinical studies and post-marketing case reports as well as published efficacy studies.

2.2. Data on the risk of QT prolongation

When the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, including torsade de pointes (TdP), particularly when combined with other risk factors (e.g. hypokalaemia, structural heart disease and bradycardia). TdP is a rare polymorphic ventricular arrhythmia that is characterised by delayed ventricular repolarisation and a prolongation of the QT interval.

[1] EMA press release

2.2.1. Non-clinical data

In compliance with the non-clinical QT interval prolongation guidance (ICH S7B), the MAH of the originator conducted 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). The most relevant data of these studies is described below.

2.2.1.1. In vitro hERG assay (Aptuit study VPT7288)

In this GLP-compliant hERG study, the effect of fenspiride (dissolved in DMSO 0.1%) at 0.3, 1, 3, 10 and 30 µM, on the rapid component of the delayed rectifier potassium channel was evaluated using HEK293 cells (n=4/group) stably transfected with hERG cDNA. The cardiac potassium channel, hERG recapitulates the rapid delayed rectifier current IKr in human ventricles.

Fenspiride induced concentration dependent decreases in hERG tail current of 10, 12, 24, 49 and 66%, respectively. When compared to the reduction of 12% observed in presence of vehicle (DMSO 0.1%), the inhibition of the hERG tail current in the presence of fenspiride was statistically significant at 10 and 30 µM (with actual concentrations of 8.8 and 27.9 µM, $P<0.001$).

Based on the percentage of hERG current inhibition (vehicle corrected) and using measured concentrations, fenspiride inhibited channel function at high concentration with a half maximal inhibitory concentration (IC_{50}) value of 15.14 µM.

2.2.1.2. Guinea-pigs isolated heart (Physiostim study PS18K723)

This non-GLP study on guinea pig isolated Langendorff perfused hearts involved 2 groups of 5 hearts perfused at a perfusion pressure of 55 ± 5 mmHg; one group received fenspiride (0.3, 1, 3, 10 and 30 µM) and the second group received the vehicle (DMSO 0.1%). Hearts were infused by increasing concentrations of compound, during successive 10 minutes periods. Several parameters were recorded continuously: left ventricular pressures (LVP), dP/dt max and dP/dt min, coronary flow, cardiac frequency and ECG parameters.

A slight concentration dependent decrease in heart rate was observed at 10 and 30 µM (with -11 and -16% from baseline, respectively), when compared to vehicle. Fenspiride induced concentration dependent increases in QT and QTcF intervals at 10 µM (+11% and +7% from baseline, respectively) and 30 µM (+19% and +13% from baseline, respectively), when compared to vehicle. Washout with vehicle, at the end of the fenspiride perfusions, reversed the effects observed in presence of fenspiride.

Fenspiride had no effects on coronary flow, LVP parameters when compared to time-matched values observed in presence of vehicle (DMSO 0.1%). No effect of fenspiride was observed on PR and QRS intervals, suggesting that fenspiride has no effect on sodium and calcium cardiac channels. Neither severe arrhythmias, nor contraction abnormalities such as contracture were observed.

2.2.2. Post-marketing data

Post-marketing data included individual case safety reports captured in the database of the originator MAH or EudraVigilance (EV) from spontaneous reporting or the scientific literature.

<u>QT prolongation / TdP</u>

Since the first marketing authorisation of fenspiride up to 13 March 2019, 46 cases with adverse drugs reactions (ADRs) pertaining to the SMQ "broad" QT prolongation / TdP were reported: cardiac death (1), electrocardiogram QT prolonged (7), electrocardiogram repolarisation abnormality (2), loss of consciousness (11), sudden death (2), syncope (23), TdP (3), ventricular arrhythmia (2) and ventricular fibrillation (1). The gender distribution of the patients showed a significant predominance of females (over two third of cases).

Out of the 7 cases that reported PTs belonging to the standardised MedDRA query (SMQ) TdP / QT prolongation (narrow), causality was assessed as likely in two cases (1 ECG-confirmed case of TdP with positive rechallenge and 1 intentional overdose with electrocardiogram QT prolonged), and possible in 2 cases (1 ECG-confirmed TdP and 1 electrocardiogram QT prolonged, both with a suggestive time to onset (TTO) and positive dechallenge) and doubtful (1 suspected TdP and 1 electrocardiogram QT prolonged) or unlikely (1 electrocardiogram QT prolonged) in the remaining cases. Known risk factors of TdP were present in all cases including suspected congenital long QT syndrome (2), hypokalaemia (1 confirmed, 1 suspected), co-medications e.g. clobutinol and clarithromycin (2), age >65 years (1) and female gender (4). A disproportionality analysis conducted in the EV data analysis system (EVDAS) for fenspiride on 8 February 2019 showed a significant Reporting Odds Ratio (ROR) for the PT electrocardiogram QT prolonged (ROR =4.59 [CI: 1.90 – 11.07] n=5) and TdP (ROR= 8.76 [CI: 2.81 – 27.28] n=3).

The SMQ broad search retrieved further relevant cases. Seven cases reported PTs belonging to the MedDRA high level term (HLT) ventricular arrhythmias and cardiac arrest (6) and to the MedDRA HLT ECG investigations (1) more indicative of cardiac symptoms, including 4 fatalities. Causality was assessed as likely in a fatal case of intentional overdose, where the patient's condition deteriorated to ventricular fibrillation; and possible in another case of ventricular arrhythmia (TdP or ventricular fibrillation, but not clearly stated) with syncope, with suggestive TTO and positive dechallenge, reporting also on the risk factor of suspected congenital long QT syndrome and female gender. In the 2 other fatal cases, sudden death was reported with a suggestive TTO and the hypothesis of the occurrence of fatal complex ventricular arrhythmia such as TdP induced by fenspiride could not be firmly ruled out. In the 3 further cases, including a fatal one, causality was assessed as doubtful. For the remaining 32 cases reporting on either syncope (21) or loss of consciousness (11), causality was assessed as at least possible in 15 of these cases, based on suggestive TTO and positive dechallenge.

Cardiac arrhythmias

Since the first marketing authorisation of fenspiride, 565 cases with at least one ADR pertaining to the SMQ "broad" Cardiac Arrhythmia were reported. These included 41 cases included in the SMQ broad QT prolongation/TdP search analysed above. The majority of cases retrieved reported on the already listed PTs of tachycardia (and synonyms) and palpitations. Furthermore, several unspecific arrhythmia terms were reported without any or unremarkable ECG findings together with symptoms of tachycardia, and were interpreted within the context of the known cardiac risk profile of fenspiride.

2.2.3. Discussion on the risk of QT prolongation

Results of the Aptuit non-clinical study show that fenspiride dose-dependently blocks hERG current in a mammalian cell system (HEK 293 cells stably transfected with hERG cDNa) with an IC_{50} of 15.14 µM at room temperature. It should be noted that the assay of hERG blockade was conducted at room temperature; measurement at physiological temperature would have been preferable and could have resulted in a more potent blockade as temperature can influence both channel gating and drug binding potencies. Furthermore, the "hERG bath solution" does not mention the external K+ concentration in the milieu. In addition, instead of perfusing the cells with DMSO before adding the drug dissolved in DMSO at a same final concentration the average amount of inhibition resulting from DMSO is

substracted from the effect of fenspiride (dissolved in DMSO). Therefore, the IC_{50} (15.14 µM) calculated based on results of this study may be overestimated and not fully reflect the actual power of the inhibition.

A contract research organisation (CRO) submitted as stakeholder "a risk profile of fenspiride using ion channel data and *in silico* action potential modeling" (see section on stakeholders input). This study found that fenspiride blocked hERG current with an IC_{50} value of 16.2 µM. However, this value may not be reliable and the inhibition exerted by fenspiride underestimated as the voltage clamp protocol used, does not permit to measure tail currents but only hERG currents partially inactivated/deactivating currents. This may also explain why, despite the fact that the test was performed at 37°C, the IC_{50} measured was not lower than that in the Aptuit study at room temperature.

The magnitude of the proarrhythmic potential is estimated by the ratio of the IC_{50} value of hERG blockade to the unbound therapeutic plasma level of the drug. Whilst ICH guidelines (S7 and E14) do not reference an acceptable safety margin for medicines with respect to the proarrhythmic potential, a lowest acceptable safety margin of 30 (i.e. the IC_{50} value should exceed the unbound plasma concentration of the drug by at least 30-fold) for drugs in absence of interaction with other cardiac ion channels has been proposed in several publications (Redfern, 2003 [2]; Pollard, 2010 [3]). However, facilitating risk factors such as subtle and otherwise asymptomatic genetic channelopathies for which the blocking potency of a drug may increase several folds were not taken into consideration in establishing this safety margin. Further, the safety margin should be adapted to the severity of the medical condition treated.

The MAH calculated the safety margin between the hERG IC_{50} obtained (15.14 µM) and the effective therapeutic plasma concentration for fenspiride, between 6 and 26, depending on the pharmaceutical form, the dose administered and the administration schedule (single or repeated). Notwithstanding the uncertainty related to the IC_{50} value calculation as discussed above, further points of concerns are raised regarding the calculation of the safety margin. Plasma concentrations corresponding to the maximum daily doses (i.e. three daily dosing: 240 mg from the tablet and 180 mg from the syrup formulation), which would most probably exceed the concentrations obtained during twice daily dosing (which was used for the repeated administration), were not determined by the MAH. It is not clear whether the analysis was performed at steady state plasma concentrations or not. For these reasons, the safety margins of 6-26 could have been overestimated. In any case, these constitute very low safety margins.

In conclusion, there may be situations in clinical practice (using maximum doses of fenspiride in vulnerable patients), when hERG channel blockade may already be significant at therapeutic plasma concentrations of fenspiride.

Fenspiride has been demonstrated in the Physiostim study to cause a significant and reversible QT/QTc prolongation (by +11%/+7% from baseline, respectively at 10 µM, and +19%/+13% from baseline, respectively at 30 µM) in *ex vivo* perfused guinea pig hearts. 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. QT/QTc interval prolongation was not accompanied by any events of arrhythmia or contracture on the guinea pig heart model at any assay concentration. Of note however, isolated heart of guinea pig were perfused at constant pressure instead of constant flow with heart beating spontaneously instead of paced at a fixed heart rate which leads to an underestimation, due to the necessary QT correction formula of the observed dose-

[2] Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG. Cardiovasc Res. 2003 Apr 1;58(1):32-45.
[3] Pollard CE, Abi Gerges N, Bridgland-Taylor MH, Easter A, Hammond TG, and Valentin J-P. Br J Pharmacol. 2010 Jan; 159(1): 12–21.

dependent QTc augmentations from 0.5%, 1.2%, 4.2%, 7.2% and 12.6% at concentrations ranging from 0.3 to 30 µM.

Based on its non-clinical data, the CRO stakeholder suggested that fenspiride may induce QT prolongation and increases the risk of arrhythmic events in the presence of concomitant cardiovascular risk factors but not in healthy population. Notwithstanding the limitation described above, these results support the conclusion that QT prolongation induced by fenspiride increases the risk of arrhythmic events in the presence of concomitant cardiovascular risk factors.

As both blockade of IKr and QT/QTc interval prolongation are recognised surrogate markers of TdP, altogether the non-clinical data provide sufficient evidence to establish that in humans fenspiride has a potential to prolong QT.

With regard to clinical data, post-marketing cases were identified reporting on QT prolongation, confirmed TdP and ventricular fibrillation with at least possible causal association with fenspiride use (one positive rechallenge, one intentional overdose and two with both suggestive TTO and positive dechallenge). These cases almost exclusively occurred in patients with one or more risk factors in addition to fenspiride use including female gender, suspected congenital long QT syndrome, hypokalaemia or concomitant use of medications known to prolong the QT interval; which is in line with the multifactorial nature of TdP. Indeed, as TdP is multifactorial, risk factors are additive until a threshold where the net repolarisation reserve is exhausted. Although causality was assessed as doubtful due to lack of information and the presence of other cardiovascular risk factors, a suggestive TTO should be noted in the 2 cases reporting on sudden death. A significant number of cases concerning predominantly female patients reporting on syncope and loss of consciousness should also be noted. Although differential diagnosis was not performed in these cases, TdP may manifest in the form of syncope and terminate spontaneously. Furthermore, a significant amount of reports was received on tachycardia and palpitations corresponding to the known safety profile of fenspiride. Although not reported as directly related to QT prolongation, these adverse drug reactions were frequent and further support that fenspiride has a cardiac effect. In addition, both tachycardia and palpitations are unspecific and broad terms, and may be the symptoms of several cardiac conditions ranging from benign to life-threatening. TdP may present with symptoms that are very similar to other tachyarrhythmias. Lack of ECG investigation is common among patients experiencing syncope, loss of consciousness, tachycardia and palpitations, especially when treated without HCP supervision (which is the case for OTC products), which generates uncertainty concerning the exact diagnosis. Therefore, the occurrence of TdP cases could be substantially underestimated.

In conclusion the analysis of post-marketing cases reported since the granting of the marketing authorisation altogether with the non-clinical data, showed sufficient evidence to support a causal association between occurrence of QT prolongation/TdP in patients and fenspiride use.

No clinical studies have been performed with fenspiride in humans specifically targeting the elucidation of its proarrhythmic characteristics. However, in view of the information currently available, a clinical study or other type of data collection activities may not provide additional relevant evidence on the potential proarrhythmic activity of fenspiride and the conduct of such clinical study or activities is considered not justified.

As per currently available evidence, torsadogenic potential of fenspiride may be attributed to its blockade of the IKr current via the hERG channels. Most probably, this inhibitory action alone may not be sufficient to elicit life-threatening arrhythmias, but requires a combination of other factors to induce triggered activity (EADs). These factors are currently not precisely known.

Although QT prolongation and TdP were not frequently reported with fenspiride, the unpredictability of the outcome and the potential severity of such events should also be considered.

Indeed, in the context of the available non-clinical data, the 6 cases where the contributory role of fenspiride was assessed as likely and the 2 cases of sudden death with a suggestive time to onset raise particular concern. Therefore, the risk of QT prolongation and the proarrhythmic potential is considered to be a major safety concern that needs to be addressed.

Two MAHs proposed to minimise this risk through:

- the addition of information on QT prolongation and TdP occurrence in the product information, including in particular contraindications in patients presenting risk factors predisposing to QT prolongation or using concomitantly medicines known to induce QT prolongation,
- through the dissemination of a DHPC to inform on the risk identified and to promote close monitoring of patients for the rapid detection of any cases, and
- switching the legal status for all fenspiride-containing products to “prescription only”.

The MAH of the originator did not propose any risk minimisation measure as they considered that the benefit-risk balance was no longer favourable.

When considering the proposed risk minimisation measures, the PRAC noted that some of the risk factors may be predictable but not all. Congenital long QT syndrome has an estimated prevalence of 1:2,000 to 1:20,000 (Cohagan and Brandis, 2019 [4]) and may remain clinically unapparent until the patient is exposed to a particular drug or other predisposing factor. In clinical practice, neither ECG nor measurements of potassium or magnesium levels are performed in case of benign and self-limiting common respiratory diseases, for which fenspiride is generally used. Therefore the PRAC considered that the investigations required in order to identify patients with the proposed contraindications (e.g. congenital long QT, hypokalaemia, hypomagnesemia) would be neither proportionate nor feasible for such treatment and these contraindications could not be applied in clinical practice. Changing the legal status or increasing the awareness of HCP through a dedicated letter would not allow overcoming these issues.

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 addition, there is no clinical evidence supporting the efficacy of sub-therapeutic doses.

2.3. Data on efficacy

Fenspiride is indicated as a symptomatic treatment (cough, expectoration) in benign respiratory diseases. The efficacy in this indication was supported by results of clinical trials versus placebo or active comparator submitted at the time of the initial marketing authorisation and is not questioned during the current procedure. A review of 13 studies published in the scientific literature was provided. Due to significant lack of information and methodological deficiencies, this incomplete dataset did not provide relevant evidence on the efficacy. No specific patient population benefiting particularly of fenspiride-containing medicinal products was identified. It is also noted that several alternative therapeutic options are available in the same indication.

[4] Cohagan B, Brandis D. Torsade de Pointes, https://www.ncbi.nlm.nih.gov/books/NBK459388/ last updated: 17 February 2019, accessed: 10 April 2019

3. Stakeholders input and other data

A CRO provided the results of *"a risk profile of fenspiride using ion channel data and in silico action potential modeling"* as a stakeholder submission and EMA provided the results of a query in Eudravigilance.

In the stakeholder's study the effect of fenspiride was assayed at physiological temperature (37±1°C) at 0.1, 1, 10, 30 and 100 µM, using the whole-cell variant of the patch clamp method (Crumb et al, 2016) on HEK293 cells stably transfected with hERG, human Cav1.2 and subunits, and human Nav1.5 cDNAs, respectively. Fenspiride concentration-dependently blocked hERG current with an IC_{50} value of 16.2 µM. In contrast, fenspiride had no effect on late Nav1.5 or Cav1.2 at the concentrations tested. It should be noted however that the method used to elicit the hERG currents was unconventional and whilst it may be correct determine the physiological aspects of hERG currents, it may not have estimated the correct IC_{50} and underestimated the inhibition exerted by fenspiride. This may explain why, despite the test was performed at 37°C, the IC_{50} measured by the CRO was not lower than the IC_{50} calculated in the Aptuit non-clinical study at room temperature.

The length of QT prolongation was predicted in humans using the *in silico* model of QT fingerprinting, based on *in vitro* data obtained on ion channels. Fenspiride induced 1.8 to 47.5 ms prolongation of the QT interval in the tested plasma concentration of 0.1–30 µM. It should be noted that free therapeutic plasma levels were not available to the authors. As per data from the MAH, free therapeutic plasma concentration fall in the low micromolar range following single or twice daily dosing (0.59 – 2.19 µM for the 80 mg tablets and 0.97 – 2.42 for the 60 mg syrup dose, respectively). Irrespective of experimental settings, as data obtained *in vitro* by the CRO were close to that of the Physiostim study, this *in silico* prediction may indicate that fenspiride may cause prolongation of the QT interval at therapeutic doses.

In an *in silico* model (Dutta revised O'Hara-Rudy model; Dutta, 2016 [5]) of the healthy ventricular endocardial myocyte, the authors demonstrated that fenspiride did not induce any early afterdepolarizations (EADs), despite prolonging the action potential. Nevertheless, in disease state models of hypertrophic cardiomyopathy, congestive heart failure and LQT3, EADs were elicited by fenspiride at various concentrations (at 30, 10 and 100 µM, respectively). This could support the conclusion that QT prolongation induced by fenspiride increases the risk of arrhythmic events in the presence of concomitant cardiovascular risk factors.

In addition, EMA performed a query in Eudravigilance using the PT pertaining to the SMQ TdP/QT prolongation (broad) and the SMQ cardiac arrhythmias (broad). Cases are described above as relevant in the section on post-marketing data.

4. Benefit-risk balance

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

A signal of QT prolongation/torsade de pointes (TdP) was discussed in the last PSUSA procedure (PSUSA/00001368/201804) and a potential effect of fenspiride on the QT interval could not be ruled out. Consequently the PRAC requested the MAH of the originator medicinal product to perform a hERG channel binding study to evaluate the risk of QT prolongation. The MAH was also requested to

[5] Dutta S. et al. Optimization of an in silico cardiac cell model for proarrhymia risk assessment. Computing in cardiology Conference. 2016, 43:869-872

consider, based on the results of the non-clinical investigation and any potential impact on the benefit-risk balance of fenspiride, whether a thorough QT/QTc clinical study in line with ICH E14 would be required.

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.

5. Risk management

The Committee, having considered the data submitted in the procedure was of the opinion that no feasible and proportionate risk minimisation measure would reduce the risks to an acceptable level (see section 2.2 for details on the measures reviewed).

5.1. Direct Healthcare Professional Communications/Communication plan

PRAC recommended the dissemination of a DHPC in February 2019 to inform HCPs of the recommended suspension of the marketing authorisations due to the risk of QT prolongation while the complete review was ongoing. A further DHPC was considered warranted to communicate the outcome of the complete scientific review. Therefore the PRAC adopted the wording of a DHPC, to inform HCPs of the confirmed risk of QT prolongation and potentially life-threatening arrhythmia associated with the use of fenspiride-containing medicinal products and on the decision to revoke the marketing authorisations in EU. The PRAC also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for fenspiride-containing medicinal products.
- 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.