Agence nationale de sécurité du médicament et des produits de santé

Public Assessment Report

Fenspiride

Rationale for the triggering of procedure under Article 107i of Directive 2001/83/EC on fenspiride

February 2019

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Disclaimer:

This assessment report was provided by the French Competent Authority (ANSM) at the time of the initiation of the procedure. It provides background scientific information which complements the final notification of a referral under Article 107i of Directive 2001/83/EC sent by the French Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the French Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency (EMA) through its Scientific Committees.

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 European Economic Area (EEA), fenspiride-containing products are authorised in Bulgaria, France, Latvia, Lithuania, Poland, Portugal and Romania[1].

During the Periodic Safety Update Report (PSUR) single assessment (PSUSA) of fenspiride (Procedure number: PSUSA/00001368/201804), for which France is Lead Member State, a review of the signal of QT prolongation/torsade de pointes was reviewed leading the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) to request further investigations to the Marketing Authorisation Holder (MAH).

Safety

Post-marketing data

A total of 5 cases of QT prolongation including 3 torsade de pointes were reported since the marketing authorization of fenspiride.

In addition, 2 cases of sudden death have also been reported where the cause of death is not documented but the occurrence of a possible QT prolongation and torsade de pointes could not be firmly ruled out.

In addition, disproportionality analysis of in EVDAS (dated on 08/02/2019) for fenspiride shows a significant Reporting Odd Ratio (ROR) for the PT “electrocardiogram QT prolonged” (ROR =4.59 [CI: 1.90 – 11.07] n=5) and “torsades de pointes” (ROR= 8.76 [CI: 2.81 – 27.28] n=3).

The post-marketing cases are described below:

One case of QT prolongation reported a possible positive rechallenge. The patient experienced torsades de

[1] According to available data in a Euopean database (Article 57 database).

pointes 3 days after fenspiride initiation, a probable long congenital QT was suspected but was asymptomatic until then. The symptoms were treated with isoprenaline en electrosystolic temporary training. After deliberated rechallenge of fenspiride lengthening of QT without recurrence of the torsades de pointes was observed. After 3 months of follow-up, no recurrence of torsades de pointes was reported.

The second case reported the occurrence of torsades de pointes with QT at 540ms, 6 days after initiation of both clobutinol and fenspiride. The patient had a possible long congenital QT (her sister died from sudden death) and also experienced hypokaliemia (3.3mmol/L) at the time of the event which may had contributed to the occurrence of the cardiac event. Both clobutinol and fenspiride were stopped at the same time. Clobutinol has been withdrawn worldwide because it was suspected to cause QT prolongation. The patient was also treated with dantron/calcium pantothenate which may have induced hypokaliemia and then enhanced risk of torsades de pointes. Both clobutinol and fenspiride were initiated and stopped at the same time. The patient recovered after discontinuation of the 2 suspected drugs. The reported causality was the same for clobutinol and fenspiride.

It should be highlighted that torsades de pointes and QTc prolongation caused by drugs are highly dependent on predisposing factors and occur rarely in patients with no concomitant risk factors. Therefore, in cases of torsades de pointes reported with fenspiride long congenital QT should also be considered as a risk factor and not only as a confounding factor. In addition, in the second case the role of fenspiride is not totally ruled out by reporting of co-suspected drugs and the presence of hypokaliemia. Indeed, torsadogenic drugs may have additive effect on QT prolongation and interaction of these drugs may have led to occurrence of torsades de pointes in a patient with multiple risk factors (i.e. possible long congenital QT syndrome and hypokaliemia at 3.3 mmol/L).

The third case reports a QT prolongation (QT at 360 ms and QT theoric at 265ms) the night after an overdose of fenspiride in a context of massive overdose in a suicidal attempt (ingestion of 15 tablets). The day after persistent prolonged QT was reported at 400ms (QT theoric: 380 ms). Fenspiride was the only suspected drug. At the time of the report the patient was recovering.

In the fourth case the chronology was not suggestive. Time to onset was not reported and the patient recovered while treatment with fenspiride was ongoing.

Regarding the first case of sudden death, the patient was treated with several drugs known to induce QT prolongation (i.e. clozapine and trimipramine). Nevertheless clozapine was initiated more than 140 days before the event (Chronology of trimipramine was not reported) whereas fenspiride and amoxicilline were more recently introduced (3 days before occurrence of the sudden death). Due to the close time relationship, the potential role of fenspiride in the occurrence of the sudden death could not be ruled out.

In the second case of sudden death, a 70 years old male patient with medical history of coronary artery bypass and dyspnoea exertional was treated with fenspiride, ambroxol and pristinamycin (both not known to prolong QT interval). Sudden death of the patient early in the morning after seven days of treatment. According to the information provided in this case fenspiride was the only suspected drug.

Of note, one fifth case of QT prolongation was reported after the Data Lock Point (DLP) of the last PSUR (i.e. outside the PSUSA procedure). The patient experienced weakness and arrhythmia on the first day of treatment with fenspiride. Concomitant treatments included clarithromycine (known to induce QT prolongation), salbutamol and montelukast. On the fourth day, symptoms worsened and the patient experienced hypertension and tachycardia (116 bpm) ECG QT prolonged was diagnosed by the cardiologist who suspected that fenspiride and clarithromycin would be the cause of this QT prolongation. Subsequently, fenspiride was discontinued and the patient recovered. The action taken with clarithromycin due to the event

was not reported.

In conclusion, cases reported since the marketing authorization were mainly reported with other confounding factors including concomitant administration of drugs known to prolong QT interval or other risk factor (e.g. overdose, dyskaliemia, long QT syndrome, ..). Nevertheless, due to close temporal relationship the potential effect of fenspiride on the QT interval could not be ruled out.

PRAC request for non-clinical data

In order to further investigate this signal of QT prolongation/ torsades de pointes, the MAH of the innovator, Les Laboratoires SERVIER, 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 with a discussion on the impact of these results on the benefit/risk balance and on whether a clinical study ICH E14 would be required. A worksharing procedure (WS) was recommended to ensure a common European assessment.

The PRAC recommendation was adopted by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) during its November 2018 meeting.

Assessment of the MAH response to the PRAC request

On 30 January 2019, the responses from Les Laboratoires SERVIER were submitted to the ANSM, Reference Member State, through a work-sharing procedure.

In compliance with the non-clinical QT interval prolongation guidance (ICH, S7B, 2005) the MAH evaluated fenspiride:

- in a standard *in vitro* model (hERG assay) as committed.
- in an integrated *in vitro* study on isolated and perfused guinea pig hearts to investigate its potential to prolong ventricular repolarization with ECG parameters measurement including QTc (Guinea-pigs isolated hearts).

1. *In vitro* hERG assay (Aptuit study VPT7288)

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 hERG channel blocker compound E 4031, at 0.1 µM, was used as reference in this study for inhibition of the hERG current.

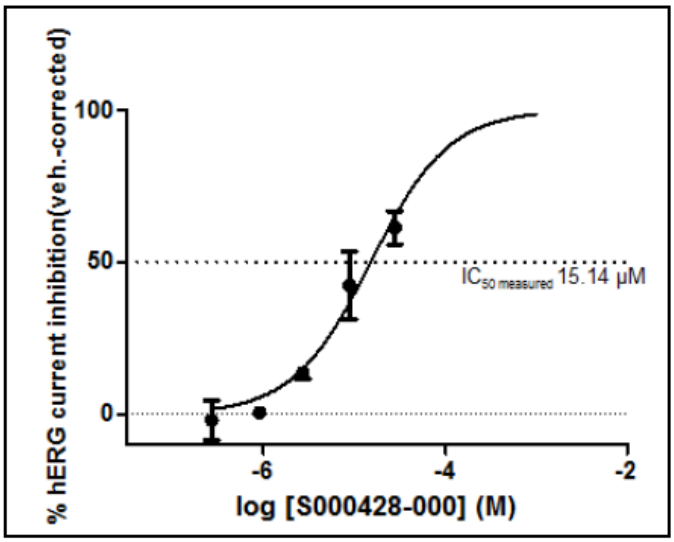
Fenspiride, tested at 0.3, 1, 3, 10 and 30 µM, induced concentration dependent decreases in hERG tail current of 10, 12, 24, 49 and 66 %, respectively. When compared to the reduction of 12 % observed in presence of vehicle (DMSO 0.1 %), the inhibition of the hERG tail current in the presence of fenspiride was statistically significant at 10 and 30 µM (actual concentrations of 8.8 and 27.9 µM, $P<0.001$).

Table (2.5.5.1.1) 1 - Effects on vehicle and of fenspiride on hERG tail current

Nominal Concentration (µM)	Measured Concentration (µM)	Tail Current (% Decrease) Not Vehicle Corrected	Tail Current (% Decrease) Vehicle Corrected
0.1% DMSO (vehicle)		**11.93±8.0**	
fenspiride 0.3 µM	0.27 µM	10.2 ± 5.8	-1.9±6.6
fenspiride 1 µM	0.9 µM	12.3 ± 0.9	0.5±1.0
fenspiride 3 µM	2.7 µM	23.9 ± 1.9	13.5±2.1
fenspiride 10 µM	8.8 µM	49.2 ± 9.8 ***	42.4±11.1
fenspiride 30µM	27.9 µM	65.9 ± 4.9***	61.3±5.5

Data are given as mean ± s. e. m. for n=4 cells, before and after correction from the mean effect in presence of vehicle
****: p<0.001 (Dunnett test)*

Figure (2.5.5.1.1) 1 - Concentration response relationship for fenspiride on hERG currents



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

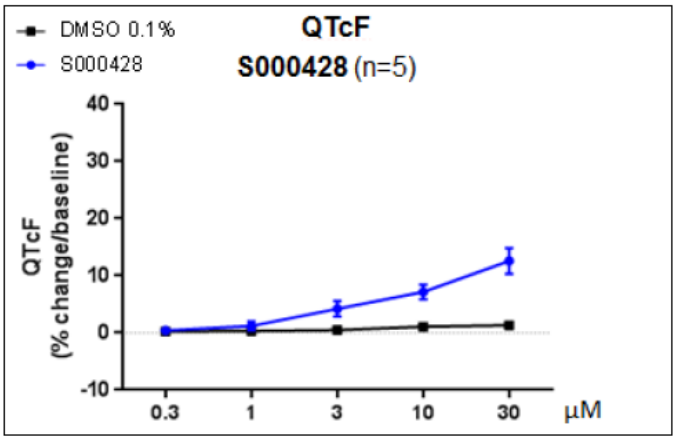
2. Guinea-pigs isolated heart (Physiostim study PS18K723)

The objective of this *in vitro* safety pharmacology study, not conducted according to the Good Laboratory Practices (non GLP), was to assess the effects of fenspiride on cardiac function on isolated Langendorff perfused guinea pig hearts. The study 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.

The results showed that:

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

Figure (2.5.5.1.2) 1 - Effects of fenspiride on QTcF, interval of isolated and perfused guinea pig hearts, with post-perfusion measured concentrations (µM)



3. Conclusion on new non-clinical findings

In vitro, 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 QTc intervals in isolated and perfused guinea pig hearts. No effect of fenspiride was observed on PR and QRS intervals, suggesting that fenspiride has no effect on sodium and calcium cardiac channels.

Based on the hERG IC_{50} value observed in the *in vitro* hERG assay (=15.14µM), the MAH provided the calculated safety margins between the hERG inhibition concentration and the effective therapeutic plasma concentration, which is 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.

However, it should be noted that according to the Product Information of the originator product PNEUMOREL, the maximum recommended dose could extend to 80mg t.i.d. and therefore the safety margin calculated for repeated administration by the MAH for repeated administration could be overestimated.

Based on the above results, it is likely that the conduct of a clinical ICHE14 study in humans would provide similar conclusions at the maximal recommended dose and above.

The ANSM also acknowledged that the MAH Les Laboratoires SERVIER reached the same conclusions and, based on the overall data, concluded that the benefit-risk ratio of this product is no longer considered favorable and informed the ANSM of their intention to withdraw the marketing authorisations of their product Pneumorel worldwide.

Efficacy

Fenspiride is indicated as a symptomatic treatment (cough, exacerbation) in benign respiratory diseases.

The efficacy in this indication has been formerly studied in studies versus placebo or comparator conducted at the time of the national marketing authorisation applications. . Those studies were conducted with the methodology and requirements of that time. Pneumorel is not considered as an essential medication.

Benefit-risk evaluation and recommendations

The ANSM considers that these new nonclinical findings, together with the accumulated postmarketing experience, support that fenspiride can prolong the QTc interval in humans. Taking into account that fenspiride is not an essential medication used in benign respiratory diseases, the ANSM concluded that the benefit-risk ratio of fenspiride-containing medicinal products is no longer considered favorable 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 initiated an urgent Union procedure under Article 107i of Directive 2001/83/EC and referred 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.