NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by France:

Product Name(s) in the Referring Member State, if applicable	STRESAM and generics
Active substance(s)	Etifoxine (hydrochloride)
All Pharmaceutical form(s)	Capsule
All Strength(s)	50 mg
All Route(s) of Administration	Oral
<Applicant(s)/Marketing Authorisation Holder(s)> in the referring Member State>	BIOCODEX ATHENA PHARMACEUTIQUES

Background

STRESAM 50 mg, capsules is indicated for the treatment of psychosomatic manifestations of anxiety.

Triggering of this referral is made in the following context:

2012: review of the benefit/risk ratio of STRESAM in France.
In view of all the data and studies available, the benefit/risk ratio was considered positive on condition that the information relative to risk indicated in the MA for this medicinal product be updated and reinforced (update of SmPC, DHPC) and that the MAH conduct the following additional studies:

- A study versus placebo and lorazepam in the indication "adjustment disorders with anxiety" in accordance with DSM-IV criteria.
- A study of dependence versus benzodiazepines.
- An investigation of drug interaction signals with anticoagulants and another with oral contraceptives.

In 2015, analysis of results of the *in vitro* study examining interactions between etifoxine and anticoagulants (warfarin and fluindione) or oral contraceptives (ethinyl-estradiol and norethisterone) did not result in a request for a study in humans.

In 2018, results of the new study (AMETIS study) provided to France (ANSM) by the MAH.
AMETIS study: evaluation of the efficacy of etifoxine compared to placebo as monotherapy in the treatment of adjustment disorders with anxiety.

The reassessment of the benefit/risk ratio of STRESAM was performed in France in light of the results from the AMETIS study.

Issues to be considered

This referral is triggered based on (i) the results of the new (AMETIS) study, which robustly suggest that etifoxine in terms of efficacy is very close to a placebo (ii) the safety profile of etifoxine that remains unchanged despite risk mitigation measures that were initiated in 2014,

Efficacy

The review of the efficacy data for etifoxine included the analysis of the final clinical report of the AMETIS (ETI178) study. Its aim was to assess the efficacy of etifoxine versus placebo, as monotherapy in the treatment of adjustment disorders with anxiety. The AMETIS study was a multicentre, randomised, double-blind, placebo-controlled clinical study with an active comparator (lorazepam) conducted in parallel groups.
Among 620 patients in this study, there were around 250 in each etifoxine and placebo group and 130 in the lorazepam group.

- After 4 weeks of treatment, this study did not demonstrate any significant difference in terms of efficacy between etifoxine and placebo in a population of patients presenting adjustment disorders with anxiety. A reduction in the total score on the HAM-A score of -12.7 ± 6.8 and -12.0 ± 7.4 in the etifoxine and placebo groups, respectively, was observed.

- A marked placebo effect was demonstrated with a HAM-A score that was halved, on average, between the beginning and end of the study (decrease was of the same magnitude as following treatment with etifoxine or lorazepam).

- A clinical improvement was also observed in the group taking lorazepam, the positive reference in the study, with a HAM-A score decreasing from 25.6 ± 4.5 on D1 to 12.5 ± 7.1 on D28.

- A ≥ 50% reduction in total HAM-A score on D28 and D35 compared to its value on D1 was observed in more than 50% of subjects treated with etifoxine and lorazepam, as well as in the placebo group. The percentage of responders in the etifoxine group was not statistically (NS) different from the percentage of responders in the placebo group on D28 (last day of treatment) (52.6 % etifoxine versus 50.6% placebo) and on D35 (one week after the end of treatment) (62.2 % etifoxine versus 61.6 % placebo).

- The reductions in scores on the Sheehan Disability Scale (SDS) in the 3 domains (work, social life/leisure activities and family life/home responsibilities) were by around 3 points on D28 adjusted on the basis of the D1 value in both group etifoxine and placebo (NS).

- The data transmitted by the pharmaceutical company did not demonstrate any rebound of anxiety one week after discontinuation of etifoxine treatment, in contrast with lorazepam.

- **Safety**

Review of the safety data for etifoxine included the following: analysis of the PSUR covering the period 20/10/2014 – 19/10/2017, safety data covering the period 01/01/2013 – 31/10/2018, data from the French national addiction vigilance network with data cut-off on 24/01/2019 and safety data from the AMETIS (ETI178) study.

- Scores obtained on the benzodiazepine withdrawal scale (CIWA-b) did not demonstrate any significant difference between the placebo group and etifoxine treatment. The difference between the

positive control (lorazepam) and placebo was on the border of significance. The risk of withdrawal related to etifoxine treatment seems to be lower than that for lorazepam. However, this study did not enable a conclusion to be reached with respect to the risk of withdrawal in the event of prolonged etifoxine use for more than 28 days.

- Vigilance data related to addiction are scarce. They indicate a potential for etifoxine abuse and dependence, which however appears lower than for benzodiazepines.

- The analysis of pharmacovigilance data by a pharmacovigilance centre and the ANSM did reveal persistent safety problems in spite of the risk minimisation measures put in place in 2012-14 (SmPC update and DHPC). Data confirmed adverse reactions that were previously identified:

- Risk for dermatological conditions, with a specific mention for serious toxic skin eruptions, such as DRESS (drug reaction with eosinophilia and systemic symptoms), AGEP (acute generalised exanthematous pustulosis) or erythema multiforme,
- Risk for liver injury, in particular acute cytolytic hepatitis.
- Metrorrhagia mostly in women also using oral contraceptives, without a clear mechanism being elucidated.
- Very rare cases of lymphocytic colitis.
- Persistence of notifications suggesting an enzyme induction phenomenon with vitamin K antagonists, methadone and levothyroxine.

Considering that the safety profile of etifoxine includes rare but potentially serious dermatological (serious toxic skin eruptions, such as DRESS, AGEP or erythema multiforme) and hepatic adverse reactions (acute cytolytic hepatitis), France considers that the new results from the AMETIS study question the B/R balance of STRESAM

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

Signed [redacted]

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ANSM

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