# Annex II

# Scientific conclusions

## Scientific conclusions

In 2012, the French National Competent Authority (L'Agence nationale de sécurité du médicament et des produits de santé, ANSM) performed a review of the benefit-risk (B-R) balance of the medicinal product Stresam (containing the active substance etifoxine), which is indicated for the treatment of psychosomatic manifestations of anxiety.

In view of the overall data available at the time, the benefit-risk balance was considered positive on condition that information relative to the risks associated with the use of etifoxine would be updated and further reinforced with updates of the product information (PI) and circulation of a Direct Healthcare Professional Communication (DHPC). The marketing authorisation holder (MAH) was also required to the 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.

The MAH conducted the above-mentioned studies. In 2015, the analysis of results of the *in vitro* study examining interactions between etifoxine and anticoagulants (warfarin and fluindione) or oral contraceptives (ethinylestradiol and norethisterone) did not result in a request for a study in humans.

Furthermore, ANSM assessed the results of the study of dependence versus benzodiazepines and concluded that said results suggests that the risk of withdrawal related to etifoxine treatment seems to be lower than for lorazepam. However, the study did not permit to reach a conclusion regarding the risk of withdrawal in case of etifoxine use for more than 28 days.

In 2018, results of a new study versus placebo and lorazepam in the indication "adjustment disorders with anxiety" (AMETIS study) were provided to ANSM by the MAH. The AMETIS study evaluated the efficacy of etifoxine compared to placebo as monotherapy in the treatment of adjustment disorders with anxiety.

ANSM considered that the results from the AMETIS study questioned the B-R balance of etifoxine and initiated a reassessment of the benefit-risk balance of etifoxine.

On 27 May 2021, France triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Stresam (etifoxine) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

**Overall summary of the scientific evaluation**

Results of pre-marketing studies showed that etifoxine appears similar or superior to active comparators or placebo in the treatment of various types of anxiety. However, although randomised and double-blind, these were small and monocentric studies conducted in 1970s and have several methodological limitations, such as lack of a placebo arm in three studies, no anxiety validated scales (except one study) and heterogeneity of the population included.

In all the studies conducted post-marketing, the HAM-A score in the etifoxine group markedly reduced between the beginning and end of the study. There are however, some uncertainties regarding the absolute effect of etifoxine because STRETI, ETILOR and ETIZAL studies have been conducted without a placebo arm, in patients with more severe ADWA at inclusion, with a lower etifoxine dosage (ETILOR, ETIZAL), and with a lower number of participants to that in the AMETIS study.

In the AMETIS study after 4 weeks of treatment, the decrease in the HAM-A score in the etifoxine group was marked at the end of the 4-week treatment period. This result was comparable to that observed in the ETILOR study (from 25.2 to 11.4) conducted in patients with the same condition. However, a statistically significant difference in terms of primary and secondary efficacy between etifoxine and placebo in the population of patients with adjustment disorder with anxiety was not demonstrated. In addition, a statistical superiority of the lorazepam (active comparator) group compared to the placebo group had not been reached. Moreover, the placebo effect shown in the AMETIS study was greater than expected based on the data published in literature and this question the ability of the study to demonstrate the "absolute" efficacy of etifoxine.

As compared to benzodiazepines, overall, the results of clinical trials suggest that one week after discontinuation of the treatment (Day 35) with etifoxine does not appear to be a rebound of anxiety. However, these results should be interpreted with caution as this was evaluated only at Day 35 and not at later time points.

A cumulative review of the safety profile of etifoxine was performed. This review included that from clinical trials, post-marketing setting and literature. The safety profile of etifoxine includes rare but potentially serious dermatological and hepatic adverse reactions. However, these can be appropriately managed by warnings in the SmPC.

The CHMP considered that due to the known risk of very rare but serious dermatological and hepatic reactions, etifoxine should be contraindicated in patients who have had severe cases of hepatitis or cytolytic hepatitis and, severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine, and section 4.3 of the SmPC as well as the package leaflet should be amended.

The CHMP also considered that the safety data reviewed was generally in accordance with the known profile of etifoxine. However, in order to complement the information already available, the CHMP considered that sections 4.4 and 4.8 should be amended to provide further information for patients and prescribers on the occurrence of severe dermatological reactions, severe hepatic reactions, lymphocytic colitis and metrorrhagia and how to manage them in the clinical setting. Amendments to the package leaflet were recommended accordingly.

The CHMP considered that the AMETIS study presented some limitations which raised concerns on the validity of the trial results. The study failed to show superiority of etifoxine versus placebo, however, the absence of any difference between the placebo group and the lorazepam group, used as a positive reference in the study, suggests that this trial lacked assay sensitivity. Thus, the results are not considered robust enough to establish that etifoxine lacked efficacy.

CHMP, having assessed the totality of the data, considered that no new evidence was available to support overturning the benefit-risk balance of etifoxine. However, CHMP considered further that the failure of the AMETIS study to show the superiority of etifoxine versus placebo raised, despite the limitations of said study, sufficient concerns on the efficacy of etifoxine to justify requesting the MAH to obtain further evidence on the effect of etifoxine as a post-authorisation efficacy study (PAES). Also, CHMP noted the limitations of the post-approval studies (discussed above).

Therefore, the MAH should conduct and submit the results of a well-designed and adequately powered randomised placebo-controlled clinical trial to assess the efficacy of etifoxine, using validated scales to measure manifestations of anxiety.

In view of the above, the CHMP concluded that the benefit-risk balance of etifoxine is favourable subject to the condition to the marketing authorisations and changes to the product information as described above.

**Grounds for CHMP opinion**

Whereas

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for Etifoxine for use in the treatment of psychosomatic manifestations of anxiety.
- The CHMP considered the totality of the data submitted by the marketing authorisation holder of etifoxine in response to the CHMP questions, including the clinical study report for the AMETIS study.
- The CHMP considered that the AMETIS study presented some limitations which raised concerns on the validity of the trial results. The study failed to show superiority of etifoxine versus placebo, however, the absence of any difference between the placebo group and the lorazepam group, used as a positive reference in the study, suggests that this trial lacked assay sensitivity. Thus, the results were not deemed sufficiently robust to establish that etifoxine lacked efficacy in the authorized indication.
- The CHMP considered further that given the failure of the AMETIS study to show the superiority of etifoxine versus placebo, a new post-authorisation efficacy study should be performed.
- The CHMP considered that due to the known risk of very rare but serious dermatological and hepatic reactions, etifoxine should be contraindicated in patients who have had severe cases of hepatitis or cytolytic hepatitis and, severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine, and section 4.3 should be amended.
- Finally, the CHMP considered that the safety data reviewed was generally in accordance with the known profile of etifoxine. However, in order to complement the information already available, the CHMP considered that sections 4.4 and 4.8 should be amended to provide further information for patients and prescribers on the occurrence of severe dermatological reactions, severe hepatic reactions, lymphocytic colitis and metrorrhagia and how to manage them in the clinical setting.

**CHMP opinion**

The CHMP, as a consequence, considers that the benefit-risk balance of etifoxine remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for etifoxine.