EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

INN/active substance: etifoxine

Procedure number: EMEA/H/A-31/1509

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Information on the procedure

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.

2. Scientific discussion

2.1. Introduction

Stresam (etifoxine) 50 mg capsule has been authorized and marketed since 1979 for the treatment of psychosomatic manifestations of anxiety such as "autonomic dystonia, notably of a cardiovascular nature". At the start of this referral procedure, Stresam was approved in 53 countries worldwide, including four countries from the European Economic Area (EEA): Bulgaria, France, Malta and

Romania. The main approved indication in these countries is "psychosomatic manifestations of anxiety".

The recommended dose of etifoxine is 3 to 4 capsules a day divided in 2 or 3 doses. Treatment duration is limited from a few days to a few weeks.

Etifoxine produces its anxiolytic effects by a dual mode of action including direct positive allosteric modulation of the GABA A receptor complex and by stimulating the synthesis of 3α-reduced neurosteroids, the most potent endogenous allosteric modulators of GABA A receptor function. This dual mechanism causes an overall inhibitory effect on neurotransmission. Although the inhibitory effect produced is similar to that of benzodiazepines, etifoxine is acting at a different target site such as β2 and β3 subunits of the GABA A receptor complex. Moreover, it targets the mitochondrial TSPO thereby leading to neurosteroid-mediated potentiation of GABA A receptors (Poisbeau et al., 2018)[1]. Emerging data from the literature also suggest that etifoxine possesses neuroprotective, neuroplastic, and anti-inflammatory properties (Nuss et al. 2019)[2].

The atypical mechanism of action of etifoxine supports clinical results obtained from post-authorisation studies (STRETI, ETILOR, ETIZAL) showing non-inferiority of etifoxine versus various anxiolytic treatments in an adult population suffering from adjustment disorders with anxiety (ADWA). It might also justify the advantages over the "GABA A-related side effects" mediated by benzodiazepines with respect to less sedation, cognitive impairment, addiction and dependence.

2.2. Data on efficacy

The clinical development of etifoxine was conducted in two phases.

The first series of clinical studies included five studies and was performed in patients with various anxiety syndromes, such as anxious patients hospitalized in cardiology department, anxiety neurosis, acute episode of anxiety, reactive anxiety, overemotional or psychasthenic patients with cardiovascular disorders. These studies were part of the initial marketing application for Stresam in 1979 in France. Results generally showed that etifoxine has similar or superior efficacy to active comparators or placebo for treating anxiety.

A second series of three post-authorisation studies, namely the STRETI study (Servant et al. 1998)[3], ETILOR study (Nguyen et al. 2006)[4] and ETIZAL study (Stein, 2015)[5], were performed by the MAH to demonstrate the efficacy and safety of etifoxine (vs. active comparators) in patients with ADWA. The decrease of anxiety was generally assessed by the Hamilton Rating Scale for Anxiety (HAM-A) or by other validated scales. A mean decrease in the HAM-A score > 50% was consistently observed in the STRETI study, in the ETILOR study and in the ETIZAL study, all after 28 days of treatment with etifoxine hydrochloride. These clinical studies have been conducted in the absence of a placebo arm, which can be a limitation given the recognised placebo-mediated psychobiological effect in both laboratory and clinical settings, especially in a vulnerable psychiatric population.

[1] Pierrick Poisbeau, Geraldine Gazzo & Laurent Calvel (2018) Anxiolytics targeting GABAA receptors: Insights on etifoxine, The World Journal of Biological Psychiatry, 19:sup1, S36-S45, DOI: 10.1080/15622975.2018.1468030
[2] Nuss P, Ferreri F, Bourin M. An update on the anxiolytic and neuroprotective properties of etifoxine: from brain GABA modulation to a whole-body mode of action. Neuropsychiatr Dis Treat. 2019;15:1781-1795. Published 2019 Jul 3. doi:10.2147/NDT.S200568
[3] Servant D, Graziani PL, Moyse D, Parquet PJ. Traitement du trouble de l'adaptation avec anxiété: évaluation de l'efficacité et de la tolérance de l'étifoxine par un essai en double aveugle contre produit de référence [Treatment of adjustment disorder with anxiety: efficacy and tolerance of etifoxine in a double-blind controlled study]. Encephale. 1998 Nov-Dec;24(6):569-74. French. PMID: 9949940.
[4] Nguyen N, Fakra E, Pradel V, Jouve E, Alquier C, Le Guern ME, Micallef J, Blin O. Efficacy of etifoxine compared to lorazepam monotherapy in the treatment of patients with adjustment disorders with anxiety: a double-blind controlled study in general practice. Hum Psychopharmacol. 2006 Apr;21(3):139-49. doi: 10.1002/hup.757. Erratum in: Hum Psychopharmacol. 2006 Dec;21(8):562. PMID: 16625522.
[5] Stein DJ. Etifoxine versus alprazolam for the treatment of adjustment disorder with anxiety: a randomized controlled trial. Adv Ther. 2015 Jan;32(1):57-68. doi: 10.1007/s12325-015-0176-6. Epub 2015 Jan 27. PMID: 25620535; PMCID: PMC4311065.

More recently, the AMETIS study was conducted with the aim to assess efficacy vs. placebo as monotherapy in patients with ADWA. The main results from this study, which triggered this referral, are presented below.

AMETIS study

Table 1 - Overview of key efficacy data (from the AMETIS study)

Sponsor	BIOCODEX
Experimental drug	Stresam®
Active substance	Etifoxine
Research title	Multicenter, randomized, double blind, parallel group clinical study to evaluate the efficacy of etifoxine monotherapy compared to placebo in the treatment of Adjustment Disorders with Anxiety.
Number of centers	99 investigation centers in metropolitan France.
Study duration	Date of inclusion of first patient: 13/04/2015 Date of final visit of last patient: 14/08/2017
Clinical phase	Phase IV
Context	The clinical efficacy of etifoxine compared to placebo for the treatment of stress-related anxiety and its physical manifestations has been demonstrated in two double-blind studies (Serradimigni 1978, Lekieffre 1979). The French health authority (*Agence Nationale de Sécurité des Médicaments*, ANSM) requested a new placebo-controlled study to be conducted for the indication "Adjustment Disorders with Anxiety" as defined by the DSM-IV.
Objectives	**Primary objective** Demonstrate a greater decrease in anxiety assessed using a score on the Hamilton anxiety rating scale (HAM-A) in patients treated with etifoxine compared to those on placebo, after 4 weeks of treatment. **Secondary objectives** Evaluate clinical improvement of patients using psychometric scales (Self-Rating Depression Scale (SDS), Clinical Global Impression (CGI) rating scales); Describe the adverse events that occurred in each treatment group during the study; Search for a possible anxiety rebound after stopping the treatment (at D28) and/or potential withdrawal effect (at D35).
Type of study / Methodology	Multicenter, randomized, double-blind clinical study comparing three parallel groups, monitored and treated as outpatients.
Number of subjects	**Planned number of patients included:** - 625 patients included in total according to a randomization ratio of 2:2:1 - 250 patients in the etifoxine group (eti) - 250 patients in the placebo group (pbo) - 125 patients in the lorazepam group (lor) **Number of patients analyzed:** - Safety Set (SS): 620 (eti: 244; pbo: 247; lor: 129) - Full Analysis Set (FAS): 585 (eti: 230; pbo: 235; lor: 120) - Per Protocol Set (PPS): 523 (eti: 206; pbo: 209; lor: 108)
Inclusion criteria	- Men and women aged from 18 to 65 years - Subjects with sufficient command of the French language to read, understand, and fill out the study documents. - Subjects who have read the information leaflet and signed the consent form.

	- Outpatients.
	- Subjects with ADWA as defined by the DSM-IV (309-24).
	- Subjects presenting levels of anxiety and depression such as:
	  - Score ≥ 20 on the Hamilton Anxiety Rating Scale HAM-A.
	  - Score < 16 on the MADRS scale.

Sponsor	BIOCODEX
	- Subjects likely to comply with the protocol, in particular taking the treatment daily. - Subjects registered with or beneficiaries of a social security scheme.

Exclusion criteria	- Subjects with a known concomitant psychiatric condition or in whom one of the following was detected during the MINI International Neuropsychiatric Interview:
	  - Major depressive episode;
	  - Suicidal risk;
	  - Hypo-manic or manic episode;
	  - Generalized anxiety;
	  - Panic disorder;
	  - Agoraphobia;
	  - Social phobia;
	  - Obsessive compulsive disorders;
	  - Post-traumatic stress;
	  - Alcohol addiction or abuse.
	- History of epilepsy.
	- Organic disorder, physiological source of anxiety (e.g. thyroid condition) or life-threatening.
	- Known or suspected drug addiction or abuse, or currently undergoing withdrawal.
	- Pregnant or breastfeeding women, sexually active women of child-bearing age using no method of contraception considered as effective by the investigator, specifically:
	  - Hormonal contraception (oral, transdermal, vaginal, sub-cutaneous, injectable);
	  - Intrauterine device;
	  - Tubal ligation;
	  - Barrier contraceptive combined with a spermicide.
	- Regular intake (more than twice a week) of a hypnotic or anxiolytic treatment (benzondiazepines, zolpidem, zopiclone), including phytotherapy, the month before the study.
	- Intake of a psychotropic drug (antidepressant, neuroleptic, mood stabilizer), including hypericum, during the four months preceding the study.
	- Regular treatment likely to interfere with the metabolism of the study treatments (carbamazepine, phenytoin, primidone, rifampicin, griseofulvin, phenobarbital, probenecid) during the study.
	- During the study, intake of beta-blockers or drugs of which the effects on the central nervous system (central depressants for example) are likely to modify the results of the study.
	- Contraindications to etifoxine as defined in the current SPC.
	- Contraindications to lorazepam as defined in the current SPC.
	- Known lactose intolerance.
	- Subjects participating in another clinical trial at the same time or in the exclusion period following recent participation in a trial.
	- Subject under guardianship.

Study treatments	Etifoxine (Stresam, 50 mg capsule) administered 3 times a day at the usual dose of 200 mg per day (50-50-100 mg), thus 4 capsules per day for 28 days.
Comparator treatment	Placebo (capsule identical to that of Stresam) administered 3 times a day, thus 4 capsules per day for 28 days.
Reference treatment	Lorazepam (capsule identical to that of Stresam) administered 3 times a day at the usual dose of 2 mg per day (0.5-0.5-1 mg), thus 4 capsules per day for 28 days.

Sponsor	BIOCODEX

Investigation procedure / Organization	D-5: Screening visit (5 days ± 2 before D1)
	- Review of information leaflet and signing of consent form.
	- Verification of diagnosis of ADWA, MINI International Neuropsychiatric Interview.
	- Verification of inclusion and exclusion criteria, in particular administration of HAM-A and MADRS scales.
	- Collection of demographic data and general clinical examination.
	- Recording of medical history and concomitant treatments.
	- Appointment scheduled for inclusion visit.
	D1: Inclusion visit
	- Administration of HAM-A and MADRS scales.
	- Overall verification that the patients still meet the inclusion and exclusion criteria.
	- For the patients included:
	  - Administration of SDS and CGI scales.
	  - Distribution of study treatments.
	D7: Telephone call from physician (7 days ± 2 after D1)
	- Verification of compliance with protocol and treatment.
	- Recording of possible adverse effects.
	D28: End of treatment visit (28 days ± 3 after D1)
	- Recovery of treatment units, used or not.
	- Administration of HAM-A scale.
	- Administration of SDS and CGI scales.
	- Administration of CIWA-b scale.
	- Recording of possible adverse effects.
	D35: End of study visit (7 days ± 2 after D28)
	- Administration of HAM-A scale.
	- Administration of SDS and CGI scales.
	- Administration of CIWA-b scale.
	- Recording of possible adverse effects.

Evaluation criteria	Primary efficacy criterion: - HAM-A score at D28 adjusted for D1 value. Secondary efficacy criteria: - Percentage of responsive patients at D28 and D35 (decrease ≥ 50% of HAM-A score in relation to D1 value) or in remission (HAM-A score □7) at D28 and D35. - HAM-A score at D35. - Somatic and psychic anxiety sub-scores on HAM-A scale at D28 and D35. - Score on CGI scales at D28 and D35. - Score on SDS scales at D28 and D35. Safety criteria: - Frequency and nature of adverse events. - Search for an anxiety rebound estimated by the change in HAM-A score between D28 and D35. - Search for a withdrawal effect estimated by the CIWA-b scale.
Statistical analysis	All the analyses planned were described in the study Statistical Analysis Plan. The main analysis concerned the FAS population and the PPS population (sensitivity analysis). It consisted in a variance-covariance model (ANCOVA) aiming to show the superiority of etifoxine compared to placebo according to the HAM-A score at D28. In the model, the variable to be explained was the HAM-A score at D28, the predictor was the treatment group (etifoxine / placebo), and the covariable was the HAM-A score at D1. Three analyses were conducted in accordance with the protocol: two intermediary

Sponsor	BIOCODEX
	analyses conducted when 50% and 75% of the values of the main criterion were available and a final analysis.
Main results	Efficacy: Primary objective: No significant difference was observed for the decrease in anxiety evaluated using the HAM-A scale in patients treated for 4 weeks with etifoxine compared to those taking a placebo despite a decrease ≥ 50% in the total HAM-A score at D28 and D35 in over 50% of patients per group. Likewise, for patients treated for 4 weeks with lorazepam, no significant difference was observed for the decrease in anxiety evaluated on the HAM-A scale compared to those taking a placebo despite a decrease ≥ 50% in the total HAM-A score at D28 and D35 in over 50% of patients per group. Secondary objectives: For all the secondary efficacy evaluation criteria, whether at D28 or D35, no statistically significant difference was observed between the etifoxine group and the placebo group or between the lorazepam group and the placebo group. Safety: Adverse events (AE) that occurred in each treatment group during the study: Most of the patients in this study did not experience any AE and no deaths were reported during the study. Overall, more patients reported an AE in the lorazepam group (24%) than the etifoxine group (19.3%), and in the lorazepam and etifoxine groups than in the placebo group (12.6%), particularly during the period when receiving the treatment. Anxiety rebound after stopping the treatment (at D28) and/or a possible withdrawal effect (at D35): When the treatment was stopped, a statistically significant anxiety rebound was observed for the lorazepam group compared to the etifoxine group and the placebo group. No difference was observed between the etifoxine group and the placebo group. At D35, no withdrawal symptoms were observed with etifoxine compared to the placebo group.

Demographic and clinical characteristics at baseline are described in the table below.

Table 2 - Baseline demographic data (Safety Set)

	Etifoxine	**Placebo**	**Lorazepam**	**Total**
N	244	247	129	620
Age: mean (SD) [min- max]	44 (13)	42 (13)	43 (13)	43 (13)
Women (%)	[18-85]	[18-83]	[19-64]	[18-85]
MADRS: mean score (SD)	67.6	66.0	71.3	67.7
	11.1 (2.9)	11.2 (3.0)	10.6 (3.1)	11.0 (3.0)
HAM-A total score: mean (SD) [min-max]	25.5 (4.0)	25.4 (3.9)	25.6 (4.5)	25.5 (4.1)
	[18-38]	[20-37]	[20-49]	[18-49]

Table 3 - HAM-A total score (FAS)

	Etifoxine(N=230)	Placebo(N=235)	Total (N=465)
Score at D1 Mean (SD) Median Min. ; Max.	25.3 (3.8) 25.0 [20 ; 38]	25.3 (3.8) 25.0 [20 ; 37]	25.3 (3.8) 25.0 [20 ; 38]
Score at D28 Mean (SD) Median Min. ; Max.	12.7 (6.5) 12.0 [0 ; 38]	13.3 (7.0) 13.0 [0 ; 41]	13.0 (6.8) 13.0 [0 ; 41]
Difference between D1 and D28 Mean (SD) Median Min. ; Max.	-12.7 (6.8) -13.0 [-31.0 ; 6.0]	-12.0 (7.4) -12.0 [-30.0 ; 21.0]	-12.3 (7.1) -12.0 [-31.0 ; 21.0]

The primary efficacy endpoint was the HAM-A total score at D28 adjusted for its value at D1 on FAS. It was analysed with an ANCOVA with the treatment group as fixed factor and the value at D1 (baseline) as covariate.

HAM-A score at D28 was lower in the etifoxine group compared to the placebo group, but this difference was not statistically significant.

The variation in the total HAM-A score between D1 and D28 showed an improvement in bothgroups with an average (± SD) decrease of -12.7 (± 6.8) points in the etifoxine group and -12 (± 7.4) points in the placebo group.

The result was identical when the analysis was conducted in the PPS population (sensitivity analysis), with a total HAM-A score in the etifoxine group 0.8 points lower than in the placebogroup (CI95%[-0.4; 2.1], p=0.2013).

Similarly, the HAM-A score at D28 was lower in the lorazepam group compared to the placebo group (the test statistic is 0.9 points), but this difference was also not significant.

The secondary endpoints included the percentage of responder patients (≥50% reduction in HAM-A score compared to its value on D1) and in remission (HAM-A score ≤7) on D28 and D35, the somatic and psychic sub scores for anxiety on the HAM-A scale on D28 and D35, the CGI (clinical global impression) scale score on D28 and D35, the SDS (Sheehan disability scale) score on D28 and D35, and the difference in HAM-A score between D28 and D35 to assess the rebound effects.

No significant difference was observed concerning the percentage of responder patients in the etifoxine group on D28 (52.6% of responders) and D35 (62.2%) compared to the placebo group (50.6% on D28 and 61.6% on D35). Also, no significant difference was observed concerning the percentage of responder patients in the lorazepam group on D28 (58.3% of responders) and D35 (53.0%) compared to the placebo group.

The reductions in scores on the SDS scale in the 3 domains (work, social life/leisure activities and family life/home responsibilities) by around 2 points on D28 and 2.5 points on D35 adjusted on the basis of the D1 value in the three groups are not significantly different between the etifoxine and placebo groups, nor between the lorazepam and the placebo groups.

The percentage of improved patients (according to the CGI scale) in the etifoxine group and lorazepam group, respectively, was not statistically different from the percentage of improved patients in the placebo group on D28 and on D35 (one week after the end of treatment).

A rebound in the HAM-A score was observed upon discontinuation of treatment in the lorazepam group. Indeed, on D35, there was a significant increase in the total HAM-A score compared to D28 in the lorazepam group (+0.6 CI95% [-0.2-1.3]), while in the etifoxine and placebo group there was a decrease in the total HAM-A score at D35 compared to D28 of -1.0 CI95% [-1.5 - -0.4] and -1.4 CI95% [-1.9 - -0.8], respectively. The mean decrease observed in the etifoxine and placebo group was statistically different from the lorazepam group ($p=0.0011$ and $p<0.0001$, respectively).

Overall, no significant difference was observed in the primary and secondary efficacy endpoints when comparing the etifoxine and placebo groups. Similarly, there was no differencebetween the lorazepam reference treatment and placebo, and the analysis did not allow to conclude that lorazepam was superior to placebo. Therefore, it can be concluded that the AMETIS study failed to discriminate superiority of etifoxine (or lorazepam) over placebo.

It should be noted that the AMETIS trial was conducted in patients with ADWA, whereas the approved indication for Stresam refers to psychosomatic manifestations of anxiety. However, this indication does not map a specific condition as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V or previous editions), rather it refers to broad-spectrum symptoms associated with different subtypes of anxiety disorders that includes ADWA.

Discussion on efficacy

In the AMETIS study, after 4 weeks of treatment, the decrease in the HAM-A score in the etifoxine group was marked and clinically significant (from 25.3 to 12.7), and 52.6% of the patients were responders 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) (Nguyen et al. 2006), but it was slightly lower than the decrease reported in the STRETI (25.4 to 9.5) (Servant et al. 1998) and ETIZAL (29.3 to 7.9) (Stein 2015) studies conducted under the same conditions, i.e. ADWA, in the same type of patients. Overall, the clinical response of the active treatments (etifoxine and lorazepam) evaluated by the Hamilton scale in the AMETIS study was therefore marked, but less than in previous studies conducted in patients with ADWA and not statistically significant. Nevertheless, all these studies showed a high homogeneity of results: patients receiving an active molecule (etifoxine or benzodiazepine) had an HAM-A score divided by 2 on average between the beginning and end of the study; this score is divided even by 3 or 4 in some studies. This marked clinical activity showed the efficacy and speed of action of these treatments in the management of ADWA. However, it should be noted that the placebo group in the AMETIS study showed a clinical effect comparable to patients receiving either etifoxine or lorazepam.

It should also be highlighted that no rebound of anxiety after etifoxine treatment withdrawal was observed in the clinical studies mentioned above. In the 3 randomized controlled studies that assessed a rebound of anxiety, the HAM-A score decreased during the week after the treatment stop (between Day 28 and Day 35) in the etifoxine-treated patients, contrarily to what was observed in benzodiazepine-treated patients in whom the HAM-A score increased between D28 and D35.

STRETI, ETILOR and ETIZAL studies demonstrate a marked decrease in HAM-A score on D28, but they 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. The lack of placebo arm in these studies is considered a shortcoming for their ability to measure the "absolute" efficacy and safety of etifoxine. In addition, taking into account the differences in the dosage used (in two studies) from the approved one, the differences in respect to the severity of the disease of the subjects included and the low number of subjects, it is considered that the level of

evidence resulting from these studies to support a beneficial effect of etifoxine in the treatment of psychosomatic manifestations of anxiety is limited.

In the AMETIS study, HAM-A score at D28 was lower in the etifoxine group compared to the placebo group, but this difference was not statistically significant. The variation in the total HAM-A score between D1 and D28 showed an improvement in both groups with an average (± SD) decrease of -12.7 (± 6.8) points in the etifoxine group and -12 (± 7.4) points in the placebo group.

The result was identical when the analysis was conducted in the PPS population (sensitivity analysis), with a total HAM-A score in the etifoxine group 0.8 points lower than in the placebo group (CI95% [-0.4; 2.1], p=0.2013).

Overall, the clinical response of the active treatments (etifoxine and lorazepam) evaluated by the Hamilton scale in the AMETIS study was marked, but less than in previous studies conducted in patients with ADWA, and not statistically significant as compared to placebo. Of note, a decrease in anxiety under placebo could be expected in the study, as a significant placebo effect has widely been reported in psychological and psychiatric disorders and is well documented in the literature. This effect can be explained by the high level of care during the study (4 consultations with the physician and 1 follow-up telephone call in 35 days). However, 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.

In conclusion, the AMETIS study failed to show superiority of etifoxine versus placebo (and lorazepam). However, the AMETIS study presented some limitations which raised concerns on the validity of the trial results. In particular, in the AMETIS study, the response to active treatment was in the lower range of existing findings, while the response to placebo was on the contrary in the upper range. Therefore, no difference was observed between the groups in terms of the decrease in anxiety assessed by the HAM-A score at the end of the study. Overall, the absence of difference between the placebo group and the lorazepam group, used as a positive reference in the study, suggests that this trial lacked assay sensitivity, and 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.

2.3. Data on safety

The International Birth Date (IBD) of etifoxine hydrochloride is 19-Jun-1979, corresponding to the first granted marketing authorization in France. Biocodex has marketed this medicinal product since January 1995. Etifoxine hydrochloride is registered worldwide via national procedures and is currently approved in 53 countries. The cumulative analysis of all safety information retrieved for Stresam was conducted up to 19-Apr-2021 and did not highlight new significant safety findings. Based on data collected through post-marketing routine safety monitoring and following measures taken in 2014, the review of available safety data for Stresam shows a constant incidence of rare but known serious side

effects over time. They include serious skin reactions, liver damage, uterine bleeding between menstrual periods in women, and inflammation of the gut (lymphocytic colitis). The MAH implemented risk minimisation measures in 2014 such as the update of the RSI to add these adverse events in section 4.8 and some warnings in section 4.4 of the SmPC. Moreover, a Direct Healthcare Professional Communication (DHPC) was sent to general practitioners, psychiatrists, and pharmacists to inform about these changes.

Key safety data are presented below.

Cumulative subject exposure in clinical trials

An overview of the studies performed for etifoxine is provided in Table 4.

During clinical trials, 839 patients were exposed to etifoxine hydrochloride. Subjects were adults over 18 years old in all studies. Most of the adult patients included in these studies were over 40 years old, except for the ETILANCE study, which included only patients between 65 and 75 years old. No study was conducted in children.

Subjects were males and females. The pharmacokinetic study and the ETIXEL study only included male healthy volunteers. Studies evaluating patients with anxiety, included more woman than men.

Table 4 - Overview of the studies performed for etifoxine

Study reference	Inclusion criteria	Number of patients	
		Etifoxine	Comparators
S.213/GB	Healthy volunteers, adults	100 to 1,500 mg single dose, N=42 (7 groups, one per dose)	Placebo, N=14 (2 subjects in each of the 7 groups)
LORETI	Healthy volunteers, adults	50 to 100 mg single dose, N = 12 + 12	Lorazepam 2 mg, N=12 Placebo, N=12
ETIXEL	Healthy volunteers, male adults	100 mg to 200 mg bid, N=22	Placebo, N=22
ETILANCE	Healthy volunteers, elderly patients	100 mg single dose, N=30	Lorazepam 2 mg, N=30 Placebo, N=30
EQUESTRE	Healthy volunteers, adults	100 mg single dose, N=32	Etifoxine base
S.137/GB	Anxiety of various origins associated with psychological and somatic disturbances and cardiovascular disorders	50 mg tid, N=14	/
S.137/GB		50 mg tid, N=30	/
S.137/GB		50 mg tid, N=25	Clobazam 10 mg tid, N=25
S.139/GB		50 mg tid, N=23	Placebo, N=24
S.132/GB		50 mg tid, N=28	Clobazam 10 mg tid, N=26
S.134/GB		50 mg tid, N=20	Clobazam 10 mg tid, N=20
S.135/GB		50 mg tid, N=23	Sulpiride 50 mg tid, N=23 Placebo, N=20
STRETI S.226/GB	ADWA HAM-A ≥ 18	150-200 mg/day, N=83	Buspirone 15-20 mg/day, N=87
ETILOR S.392/EN	ADWA HAM-A ≥ 20	50 mg tid, N=93	Lorazepam 1.5 mg/day, N = 96
ETIZAL S.650/EN	ADWA HAM-A ≥ 20	50 mg tid, N=100	Alprazolam 0.5 mg tid, N=101
AMETIS	ADWA HAM-A ≥ 20	200 mg daily, N=250	Lorazepam 2 mg daily, N=125 Placebo, N=250
Total patients		**N=839**	**N=917**

bid: *bis in die*, twice daily; tid: *ter in die*, thrice daily; DB: double-blind design; ADWA: Adjustment Disorders

The table below summarised all serious adverse events received by the MAH from clinical trials since the marketing by Biocodex.

Table 5 - Number of serious adverse events by Preferred Term (PT) from clinical trials

System Organ Class (SOC) MedDRA PT	Etifoxine hydrochloride	Blinded	Active comparator	Placebo
Ear and labyrinth disorders	**0**	**0**	**1**	**0**
Vertigo	0	0	1	0
Eye disorders	**0**	**0**	**1**	**0**
Retinal artery thrombosis	0	0	1	0
Hepatobiliary disorders	**1**	**0**	**0**	**0**
Jaundice	1	0	0	0
Injury, poisoning and procedural complications	**1**	**4**	**1**	**1**
Contusion	0	1	0	0
Ligament injury	1	0	0	0
Ligament sprain	0	1	0	0
Overdose	0	0	1	0
Road traffic accident	0	1	0	0
Wound	0	1	0	0
Injury	0	0	0	1
Musculoskeletal and connective tissue disorders	**0**	**0**	**1**	**0**
Back pain	0	0	1	0
Neoplasms, benign malignant and unspecified (incl cyst)	**1**	**0**	**0**	**0**
Fibroma	1	0	0	0
Nervous system disorders	**0**	**0**	**1**	**0**
Somnolence	0	0	1	0
Psychiatric disorders	**0**	**0**	**1**	**0**
Suicidal ideation	0	0	1	0
Surgical and medical procedures	**1**	**0**	**0**	**0**
Cervical conisation	1	0	0	0
TOTAL	**4**	**4**	**6**	**1**

Discussion on Safety

The safety profile of etifoxine is well characterized and no new significant safety findings have been brought out during this referral.

Rare serious adverse events of dermatological manifestations and hepatic disorders are already known to be associated with the use of etifoxine. They are considered as important identified risks for the product.

Regarding skin toxicity, SCARs, including erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome and Steven Johnson syndrome (SJS), occurred with reporting rate of 0.06/10,000 patients.

Severe hepatic disorders, especially cytolytic hepatitis, occurred with a reporting rate of 0.09/10,000 patients.

Both serious adverse events of dermatological manifestations and of hepatic disorders occurred at a very rare frequency. Outcome of these events was mostly favourable after drug withdrawal and no fatal events have even been reported among these cases. No new finding was identified for these risks which appears well managed in clinical practice.

However, the CHMP considered that due to the 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. Section 4.3 of the SmPC will be amended accordingly.

Five cases of very rare lymphocytic colitis were also reported.

These risks are already mentioned in sections 4.4 and 4.8 of the SmPC. However, in order to complement the information already available, these sections should be amended to update the frequency from 'unknown' to 'very rare' and to provide further information for patients and prescribers on the occurrence of these risks and how to manage them in the clinical setting.

"Metrorrhagia in women treated with oral contraceptive" is a listed reaction in STRESAM Reference Safety Information (RSI). An analysis of cases reported for etifoxine has been performed to retrieved cases of menstrual disorders. A total of 91 cases has been retrieved in BIOCODEX PV database using a selection of MedDRA Preferred Term (PT) in the SOC: Reproductive system and breast disorders. It represents a reporting rate of 0.1 for 100 000 treated patients (very rare frequency). Among these events of menstrual disorders, 74.5% referred to intermenstrual bleeding. Events were mainly reported in women with age from 18 to 40 years-old (83%), which corresponds to the main treated population with etifoxine. In addition, a high percentage of the women in this age subgroup used hormonal contraception. In summary, the cumulative review of data provides sufficient evidence to conclude on the causal relationship between etifoxine and uterine bleeding in women receiving hormonal contraception. However, this adverse event is only currently mentioned in section 4.8 of the SmPC as a very rare event. As such, it should be included as a "special warning and precaution for use" in section 4.4 of the SmPC in order to alert healthcare professionals of this risk.

The package leaflet should be updated accordingly.

2.4. Non-clinical aspects

Three studies were submitted which provided supportive data in evaluating the psychological and physical dependence potential of etifoxine in animal models.

Internal report S-122; Prof. Leuschner, 1979

This study explored the potential of etifoxine to induce psychological dependence and evaluated the frequency of intravenous self-injection in cocaine-dependent monkeys. At the doses tested (0.05, 0.1 and 0.2 mg/kg by injection IV) etifoxine did not caused psychological habituation. The frequency of self-injections was comparable to that measured with physiological sodium chloride solution. Contrarily, morphine hydrochloride was very addictive.

Internal report S-193; Huntingdon Life Sciences, 1995

In this study on physical dependence, male Sprague Dawley rats (250-275 g) were given daily increasing oral doses of etifoxine (from 150 to 500 mg/kg/day) or diazepam (from 100 to 200

mg/kg/day), chosen as a positive control, for 40 days. Withdrawal signs (agitation, jumpiness, jerking, aggressiveness, body tremor, chewing movements, etc.) were recorded under two experimental conditions: at the end of the treatment, with or without injection of flumazenil (used to precipitate the appearance of withdrawal signs).

Differently from diazepam which induced a moderate physical dependence, etifoxine hydrochloride did not elicit any adverse or spontaneous withdrawal signs. In addition, no signs of withdrawal were exhibited further to flumazenil challenge. The study results demonstrated that etifoxine did not induce physical dependence under the experimental conditions tested.

Internal report S-205; Huntingdon Life Sciences, 1996

In this third study of psychological dependence, an intragastric cannula was surgically implanted in 6 Cynomologus monkeys (3 males and 3 females; 2-4 years old; 2.2-3.5 kg). A period of 14 days was necessary to familiarize the animals with the device by alternating the administration of saline solution and vehicle; the number of lever presses showing the self-administered volume was recorded daily, as well as any side effects. A high number of voluntary self-administrations compared to control animals expresses a psychological dependence to the compound ("drug seeking behavior").

No monkeys showed a desire to repeatedly self-administer the product orally at doses of 5, 10 or 20 mg/kg. At the end of the trial (from day 57 or 86), the monkeys received 8 daily involuntary administrations of etifoxine at a dose of 20 mg/kg (i.e. 160 mg/kg/d) for 2 weeks: no signs of psychological dependence were noted. These signs were quantified by the daily average number of self-administrations close to this in vehicle group (1.7 vs 1.6 respectively).

Conclusion on non-clinical aspects

The three non-clinical studies submitted showed a lack of psychological and physical dependence upon discontinuation of etifoxine, thus highlighting the potential clinical advantage of etifoxine vs. benzodiazepines.

The different pharmacodynamic action of etifoxine compared to benzodiazepines might explain why etifoxine is devoid of a number of adverse consequences associated with the targeting of the $GABA_A$ receptors. These include impaired cognition, psychological and physical dependence, withdrawal syndrome and rebound of anxiety typically associated with BZDs use.

3. Benefit-risk balance

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), 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 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.

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 Committee considers that the benefit-risk balance of etifoxine remains favourable subject to the condition to the marketing authorisations and taking into account amendments to the product information.

4. Summary of new activities and measures

4.1.1. Risk minimisation measures

4.1.1.1. Routine risk minimisation measures

Amendments to the product information

The CHMP considered that amendments to sections 4.3, 4.4 and 4.8 of the SmPC were necessary to include the information of this review.

In addition, the CHMP considered that Stresam use should be contraindicated in patients who have had severe cases of hepatitis, cytolytic hepatitis, severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine.

Further warnings and precautions of use relating to the risks associated with the use of Stresam were also included 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.

The Package Leaflet was amended accordingly.

4.2. Other studies

The MAH shall conduct a post-authorisation efficacy study (PAES). 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 (see also section 'Condition to the marketing authorisations').

4.3. Direct Healthcare Professional Communications and Communication plan

The CHMP agreed on key messages that could be used for communication via preferred routes, to be decided nationally, e.g., bulletin, webpage or direct healthcare professional communication (DHPC). The information should be disseminated to healthcare professionals such as physicians and pharmacists (hospital and community), to inform them of the possible risks of severe dermatological and hepatic reactions associated with the use of Stresam (etifoxine).

The following key elements for communication were agreed but the exact content and presentation is to be agreed with the national competent authority of the Member States where the product is marketed:

- Severe dermatological reactions have been reported in patients receiving etifoxine with a very rare frequency. These include:
    - Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome
    - Stevens Johnson Syndrome (SJS)
    - Dermatitis exfoliative generalized

- Severe cases of cytolytic hepatitis have been reported with the use of STRESAM during post-marketing experience with a very rare frequency. Caution should be taken in patients with risk factors for hepatic disorders.

- Stresam should be immediately discontinued at occurrence of any signs of cutaneous or hepatic reactions.
- Stresam is contraindicated in patients who have had severe cases of hepatitis or cytolytic hepatitis, or severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine.

The product information will be updated with the current knowledge including new contraindications and warnings.

5. Condition to the marketing authorisations

The marketing authorisation holder for Stresam (etifoxine) shall complete the below condition, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

Post-authorisation efficacy study (PAES): 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. The final study report should be submitted to the relevant National Competent Authorities:	Within 5 years from Commission decision

6. Grounds for Recommendation

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.

In view of the above, the Committee considers that the benefit-risk balance of etifoxine remains favourable subject to the condition to the marketing authorisations and taking into account amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for etifoxine.

Appendix I - Divergent positions

Article 31 of Directive 2001/83/EC

Procedure No: EMEA/H/A-31/1509

Etifoxine-containing medicinal products

Divergent statement

The undersigned CHMP member did not agree with the CHMP's positive opinion recommending the maintenance of the marketing authorisation of etifoxine indicated in the treatment of psychosomatic manifestations of anxiety.

Reasons for divergent opinion are based on the insufficient demonstration of the efficacy profile of etifoxine together with worrying safety concerns. Overall, I consider that the MAH has not included additional relevant information to substantiate the positive benefit-risk balance of etifoxine in the current authorized indication:

- Efficacy is not demonstrated when considering results from the recent large placebo controlled AMETIS study, since this study failed to show any superiority of etifoxine versus placebo in the treatment of psychosomatic manifestations of anxiety

- The safety profile of etifoxine is of worrying concerns since despite risk minimization measures, a constant incidence of rare serious adverse effects still occurred over the time, especially serious dermatological adverse reactions (serious toxic skin eruptions, such as DRESS drug reaction with eosinophilia and systemic symptoms, Steven Johnson Syndrome, AGEP acute generalised exanthematous pustulosis or erythema multiforme), and liver injury adverse reactions (such as severe cases of acute cytolytic hepatitis). Metrorrhagia and very rare cases of lymphocytic colitis were also reported.

As a conclusion, I am of the opinion the benefit/risk ratio of etifoxine is negative in the treatment of psychosomatic manifestations of anxiety.

CHMP Member expressing a divergent opinion:

- Alexandre Moreau