EMA concludes review of anxiety medicine Stresam (etifoxine)

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Information on Stresam (etifoxine)

- Stresam is authorised in France, Malta, Bulgaria and Romania for the treatment of anxiety disorders.
- The medicine contains the active substance etifoxine. The exact way etifoxine works is not fully understood, but it is known to attach to the same targets (receptors) on nerve cells as GABA (gamma-amino butyric acid). GABA is a neurotransmitter (a chemical that nerve cells use to communicate) that blocks certain brain signals. Etifoxine mimics the effect of GABA both directly and indirectly, leading to a calming effect that helps to control the symptoms associated with anxiety.
- Stresam is available as capsules that are taken daily for a few days up to a number of weeks.
- In 2014, the French medicines agency put in place risk minimisation measures (update to the product information and a letter to healthcare professionals) to mitigate the risk of certain side effects identified at that time. The company was also asked to perform additional studies, including the AMETIS study.

The following product is authorised via national procedure.

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Etifoxine hydrochloride 50 mg	Stresam capsule	Capsule	POM	MA239/00401	Biocodex

Information from the EMA about the safety concern

- The review of Stresam was initiated in June 2021 at the request of France, under Article 31 of Directive 2001/83/EC.
- The review has been carried out by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

- EMA's human medicines committee (CHMP) has finalised its review of Stresam (etifoxine) and concluded that the medicine can continue to be used for the treatment of anxiety disorders, but it must not be used in patients who previously had severe skin reactions or severe liver problems after taking etifoxine.

- During the review, the CHMP assessed all available data on the benefits and risks of Stresam, including the results of a study (AMETIS) on the efficacy of etifoxine in treating adjustment disorders with anxiety (where people have difficulty coping with stressful events). The Committee also assessed safety data from clinical studies and post-marketing experience.

- EMA concluded that Stresam can continue to be used for the treatment of anxiety disorders in some patients, but restrictions on its use have been put in place to minimise the risk of very rare but serious side effects that may occur with etifoxine. The medicine must not be used in patients who experienced severe skin reactions (including DRESS syndrome, Stevens Johnson syndrome and generalised exfoliative dermatitis) or severe liver damage (severe hepatitis or cytolytic hepatitis) with previous etifoxine treatment, and treatment must be stopped if signs of skin reactions or liver problems appear. In patients at risk of liver problems, liver function tests should be performed before starting treatment and around one month after treatment has started. In addition, the company that markets Stresam will have to conduct a study to further characterise the effects of etifoxine in patients with anxiety.

- The product information for Stresam will be updated to include the above recommendations.

In Malta

For Healthcare Professionals

- Very rare cases of severe dermatological reactions (including DRESS syndrome, Stevens Johnson Syndrome (SJS) and generalised exfoliative dermatitis) and severe cytolytic hepatitis have been reported in patients treated with Stresam.

- Stresam is now contraindicated in patients who had severe dermatological reactions or severe cases of hepatitis or cytolytic hepatitis during previous treatment with etifoxine.

- Patients should be instructed to stop taking Stresam and seek urgent medical care if they experience:
  - severe skin or allergic reactions;
  - jaundice, vomiting, tiredness, abdominal pain, which can be indicative of severe liver problems;
  - watery diarrhoea.

- In patients with risk factors for hepatic disorders (such as elderly patients, patients with medical history of previous viral hepatitis or other conditions), liver function tests should be performed before starting Stresam and around one month after treatment initiation.

- Few cases of lymphocytic colitis have been reported with the use of Stresam. Appropriate examinations should be considered in case of watery diarrhoea during treatment.

- A letter summarising the above recommendations will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine.

Advice for Patients

Treatment with Stresam (etifoxine)

- Stresam (etifoxine) can continue to be used for the treatment of anxiety disorders.

- Stresam must not be used in patients who had serious skin reactions or liver damage following previous treatment with etifoxine.

- Patients should stop taking the medicine and seek urgent medical attention if they experience:
  - severe skin or allergic reactions;
  - jaundice (yellowing of the skin and eyes), vomiting, tiredness, abdominal (belly) pain - these could be signs of severe liver problems;
  - watery diarrhoea.

- If you are at risk of developing liver problems, your doctor will do some tests to check your liver function before starting Stresam and around one month after you start treatment.

- If you are taking Stresam and have any questions or concerns, speak to your doctor or pharmacist.

For more information please see the European Medicines Agency's press release.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance with Stresam (etifoxine). Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to http://www.medicinesauthority.gov.mt/adrportal or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate

Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

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