Product Information as approved by the CHMP on 27 January 2022, pending endorsement by the European Commission

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Product Information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the Product Information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

A. Summary of Product Characteristics

Section 4.3: Contraindications

The following wording should be added in this section:

[…]

- patients who have had severe cases of hepatitis or cytolytic hepatitis, during previous treatment with etifoxine;
- patients who have had severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine.

Section 4.4: Special warnings and precautions for use

The following wording should be reflected in this section:

Severe dermatological reactions

Severe dermatological reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, have been reported with etifoxine with a very rare frequency. The onset of skin toxicity with STRESAM usually ranged from a few days to 1 month, depending on the reactions. As per post-marketing data, outcome of skin reactions is mostly favorable after etifoxine withdrawal.No fatal outcome due to severe cutaneous adverse reactions has been reported with etifoxine. Patients should be aware of this risk of skin toxicity and cutaneous signs and symptoms should be closely monitored. After the occurrence of skin toxicity with etifoxine the medicinal product should be immediately discontinued and never reintroduced.

Severe hepatic reactions

Severe cases of cytolytic hepatitis have been reported with the use of etifoxine during post- marketing experience with a very rare frequency. As per post-marketing data, time to onset of hepatic reactions after etifoxine introduction mainly occurred between 2 weeks and 1 month of treatment. Caution should be taken in patients with risk factors for hepatic disorders such as elderly patients, patients with medical history of previous viral hepatitis or any other conditions identified on an individual basis by the practitioner. Hepatic disorders can be asymptomatic and detected only through specific laboratory tests. In patients with risk factors for hepatic disorders, liver function tests should be performed before starting etifoxine and around one month after treatment initiation. After the occurrence of liver toxicity with etifoxine, the medicinal product should be immediately discontinued and never reintroduced.

Lymphocytic colitis

Few cases of lymphocytic colitis have been reported with the use of etifoxine during post- marketing experience. Appropriate examinations should be considered in case of watery diarrhoea in patients treated with etifoxine. In case of watery diarrhoea with etifoxine the medicinal product should be immediately discontinued.

Metrorrhagia

Cases of metrorrhagia in women on oral contraceptives have been reported with the use of etifoxine in post- marketing setting.

Section 4.8: Undesirable effects

The wording in this section should be amended as follows (wording to be deleted is shown as strike through and wording to be added as underlined):

The side effects which have been reported are classified after by system-organ class and by frequency defined as: very common (>1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000) and very rare (< 1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Rare**	**Very rare**	**Unknown frequency**
Nervous System disorders	Slight drowsiness, occurring at the start of treatment and spontaneously disappearing with its continuation.		
Skin and subcutaneous tissue disorders	Skin reactions: maculo-papular rash, erythema polymorphe, pruritus, face oedema.	Allergic reactions: urticaria, Quincke's oedema Serious skin reactions: DRESS syndrome, Stevens- Johnson syndrome, generalized exfoliative dermatitis	Anaphylactic shock, ~~DRESS syndrome, Stevens-Johnson syndrome,~~ leukocytoclastic vasculitis
Hepatobiliary disorders		Hepatitis, Cytolytic hepatitis.	~~Hepatic disorders: hepatitis, cytolitic hepatitis.~~
Reproductive system and breast disorders		Metrorrhagia in women treated with oral contraceptive	~~Metrorrhagia in women treated with oral contraceptive~~
Gastrointestinal disorders		Lymphocytic colitis	~~Lymphocytic colitis~~

B. Package leaflet

Section 2: What you need to know before you take STRESAM

The following wording should be added in this section:

Do not take STRESAM

- if you have had severe liver problems, such as inflammation of the liver (hepatitis) or cytolytic hepatitis, during previous treatment with STRESAM

- if you have had severe skin reactions during previous treatment with STRESAM

Warnings and precautions

Talk to your doctor or pharmacist **before taking STRESAM**:

- 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.

You should stop taking the medicine and seek urgent medical attention if you experience the following events **during treatment with STRESAM**:

- severe skin or allergic reactions (see Section 4);
- jaundice (yellowing of the skin and eyes), vomiting, tiredness, abdominal (belly) pain - these could be signs of severe liver problems (see Section 4);
- watery diarrhoea (see Section 4).

Talk to your doctor or pharmacist if you experience bleeding from the uterus between menstrual periods (metrorrhagia) when on oral contraceptives during treatment with STRESAM.

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

Section 4. Possible side effects

The frequency of side effects in this section should be aligned with section 4.8 of the SmPC.

The following wording should be added in this section:

You should you seek urgent medical advice and you should stop immediately to take STRESAM if you 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