SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

STRESAM 50 mg capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: etifoxine hydrochloride 50 mg.

Contains sugar: lactose monohydrate 119 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

No. 2 hard gelatine capsules with blue caps and opaque white bodies. The capsules are filled with a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psychosomatic manifestations of anxiety.

4.2 Posology and method of administration

150 mg to 200 mg daily taken as 2 to 3 divided doses.

Treatment duration: a few days to a few weeks. Treatment duration may not exceed 8 weeks.

The capsules are to be taken with a little water.

4.3 Contraindications

- hypersensitivity to etifoxine hydrochloride or to any of the excipients listed in section 6.1.
- States of shock.
- Severely impaired liver and/or renal function.
- Myasthenia gravis.
- Patients who have had severe cases of hepatitis or cytolytic hepatitis, during previous treatment with STRESAM.
- Patients who have had severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with STRESAM.
- Because of the presence of lactose, this medicine is contraindicated in patients with galactosaemia, glucose and galactose malabsorption syndrome or lactase deficit.

4.4 Special warnings and precautions for use

Warnings:

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 STRESAM 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 STRESAM withdrawal. No fatal outcome due to severe cutaneous adverse reactions has been reported with STRESAM. 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 STRESAM, the medicine should be immediately discontinued and never reintroduced.

Severe hepatic reactions

Severe cases of cytolytic hepatitis have been reported with the use of STRESAM during post-marketing experience with a very rare frequency. As per post-marketing data, time to onset of hepatic reactions

after STRESAM 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 STRESAM and around one month after treatment initiation. After the occurrence of liver toxicity with STRESAM, the medicine should be immediately discontinued and never reintroduced.

Lymphocytis colitis

Few cases of lymphocytis colitis have been reported with the use of STRESAM during post-marketing experience. Appropriate examinations should be considered in case of watery diarrhoea in patients treated with STRESAM. In case of watery diarrhoea with STRESAM, the medicine should be immediately discontinued.

Metrorrhagia

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

Precautions:

Caution is advised when STRESAM is used in conjunction with central nervous system depressants. Simultaneous intake of alcoholic drinks is not advised.

4.5 Interaction with other medicines and other forms of interaction

Inadvisable combinations:

Alcohol: alcohol increases the sedative effect of these substances. Impaired alertness may make vehicle driving and machinery operations dangerous.

Avoid alcoholic drinks and medicines containing alcohol.

Combinations needing to be taken into account:

Other central nervous system depressants: morphine derivatives (analgesics, antitussives and narcotic substitutes); benzodiazepines; hypnotics; neuroleptics, sedative H1 antihistamines, sedative antidepressants; central antihypertensives; baclofen; thalidomide. The concurrent use of **STRESAM** and these agents may lead to increased central nervous system depression. Impaired alertness may make vehicle driving or machinery operation dangerous.

4.6 Fertility, pregnancy and lactation

In the absence of sufficient clinical data, the administration of **STRESAM** during pregnancy and whilst breastfeeding is not recommended

STRESAM crosses the placental barrier

Fertility:

No data on male and female fertility are available.

4.7 Effects on ability to drive and use machines

Slight drowsiness, occurring at the start of treatment with **STRESAM** and disappearing spontaneously with its continuation, has been reported.

Patients, particularly vehicle drivers and machinery operators, should be advised of the risks of drowsiness associated with the intake of **STRESAM**

4.8 Undesirable effects

The side effects which have been reported are classified 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 disappearing spontaneously with its continuation.		
Gastrointestinal disorders		Lymphocytic colitis	
Hepatobiliary disorders		Hepatitis, cytolytic hepatitis	
Skin and subcutaneous tissue disorders	Skin reactions: rash maculo-papular, polymorphe erythema, pruritus, face oedema.	Allergic reactions: urticaria, Quincke's oedema Serious skin reactions: DRESS syndrome, Stevens- Johnson syndrome, generalized exfoliative dermatitis	Anaphylactic shock, leukocytoclastic vasculitis
Reproductive system and breast disorders		Metrorrhagia in women treated with oral contraceptives	

4.9 Overdose

If an overdose is taken, gastric lavage should be performed, followed by symptomatic treatment if

necessary. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.6 Tranquillizers.

Pharmacotherapeutic group: N, Nervous system, ATC code: N05Bx03

Etifoxine hydrochloride belongs to the class of benzoxazine chemicals.

As antianxiety agent, it has an autonomic regulatory action.

In vitro and *in vivo* studies carried out in the rat and the mouse showed that the anxiolytic activity of etifoxine is due to a double mechanism of action (direct and indirect) on the GABAA receptor enhancing the GABAergic transmission:

- a direct action on the $GABA_A$ receptor by an allosteric modulation, etifoxine binds preferentially to sub-units β2 and β3; studies show that etifoxine binds to a $GABA_A$ receptor site distinct from that of benzodiazepines.
- an indirect action by the increase of the neuronal production of neurosteroids (via activation of the mitochondrial translocator protein) such as allopregnanolone, those neurosteroids being positive allosteric modulators of the $GABA_A$ receptor.

5.2 Pharmacokinetic properties

Etifoxine hydrochloride is well absorbed by oral route. It does not bind to blood cells, its plasma levels fall slowly in three phases and it is mainly eliminated in urine.

Etifoxine hydrochloride crosses the placental barrier.

5.3 Preclinical safety data

The studies performed in animals did not show any risk of pharmaco-dependence.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, purified talc.

Capsule: gelatin, titanium dioxide (E171), Indigotin blue (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

The capsules are packed into blister packs of 60 or 100 capsules (i.e. each blister strip contains twenty capsules and three (3) or five (5) blister strips are packed into a cardboard outer carton). The blister strips are heat-sealed and consist of a clear polyvinyl chloride film sealed by aluminium metallized film.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand

Johannesburg

1685

0860 ADCOCK (232625)

8. REGISTRATION NUMBER(S)

A39/2.6/0072

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 July 2006

Under license of Biocodex, France

10. DATE OF REVISION OF THE TEXT

02 August 2022