APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

STRESIGEN 50 mg capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: etifoxine hydrochloride 50 mg.

Each capsule contains sugar (lactose monohydrate 110 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule.

The hard gelatin capsule consists of a white-coloured opaque body and blue-coloured opaque cap. Capsules contain an off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STRESIGEN is indicated in psychosomatic manifestations of anxiety.

4.2 Posology and method of administration

The usual dosage of STRESIGEN is 150 mg to 200 mg daily in two to three divided doses.

STRESIGEN is prescribed for a few days to a few weeks. Treatment duration may not exceed 8 weeks

Method of administration

Oral.

Capsules should be swallowed with a little water.

Missed dose:

Medical practitioners should advise patients who forget to take STRESIGEN to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

STRESIGEN is contraindicated in the following patients:

- hypersensitivity to etifoxine hydrochloride or to any of the ingredients of STRESIGEN (see 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 STRESIGEN
- patients who have had severe dermatological reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment

with etifioxine.

4.4 Special warnings and precautions for use

Severe dermatological reactions

Severe dermatological reactions, including DRESS syndrome, SJS and dermatitis exfoliative generalized, have been reported with etifoxine, (as contained in STRESIGEN), with a very rare frequency. The onset of skin toxicity with etifoxine usually ranged from a few days to 1 month, depending on the reactions. Outcome of skin reactions is mostly favourable after STRESIGEN withdrawal. No fatal outcome due to severe cutaneous adverse reactions has been reported with STRESIGEN. Patients should be aware of this risk of skin toxicity and cutaneous signs and symptoms should be closely monitored. STRESIGEN should be immediately discontinued and never reintroduced should skin toxicity occur whilst taking this medicine.

Severe hepatic reactions

Severe cases of cytolytic hepatitis have been reported with the use of etifoxine, (as contained in STRESIGEN), with a very rare frequency. 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 medical 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 STRESIGEN and around one month after treatment initiation. After the

occurrence of liver toxicity with STRESIGEN, this medicine should be immediately discontinued and never reintroduced.

Lymphocytic colitis

Few cases of lymphocytic colitis have been reported with the use of etifoxine, (as contained in STRESIGEN). In cases of watery diarrhoea, appropriate examinations should be considered in those patients treated with STRESIGEN. Should the patient experience watery diarrhoea whilst taking STRESIGEN, the medicine should be immediately discontinued.

Metrorrhagia

In women on oral contraceptives, cases of metrorrhagia have been reported with the use of etifoxine, (as contained in STRESIGEN).

Central nervous system depressants

Because of the risk of reciprocal potentialisation:

- caution is advised when STRESIGEN is used in conjunction with central nervous system depressants
- simultaneous intake of alcoholic drinks is not advised.

Lactose intolerance

STRESIGEN contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take STRESIGEN (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not advised

Alcohol

Alcohol increases the sedative effect of STRESIGEN, impairing alertness, which may make vehicle driving and operation of machinery dangerous.

Concomitant use of alcoholic drinks and alcohol-containing medicines should be avoided.

Combinations to be taken into account

Other central nervous system (CNS) depressants

Morphine derivatives (analgesics, antitussives and narcotic substitutes); benzodiazepines; hypnotics; neuroleptics, sedative H_1 antihistamines, sedative antidepressants, central antihypertensives, baclofen; thalidomide. The concurrent use of STRESIGEN and these medicines may lead to increased central nervous system depression. Impaired alertness may make vehicle driving or machinery operation dangerous.

4.6 Fertility, pregnancy and lactation

The administration of STRESIGEN during pregnancy and whilst breastfeeding is not recommended as there is limited data available.

STRESIGEN crosses the placenta.

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 STRESIGEN therapy, disappearing spontaneously with its continuation, has been reported.

Patients, particularly vehicle drivers and machine operators, should be advised of the risks of drowsiness associated with the intake of STRESIGEN.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:

Frequent = (≥ 1/100 to < 1/10).

Less frequent = Infrequent (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000).

Frequency not known = cannot be estimated from the available data.

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent Frequency unknown	Allergic reactions (urticaria, Quincke's oedema) Anaphylactic shock
Nervous system disorders	Less frequent	Slight drowsiness, occurring at the start of therapy and disappearing spontaneously with STRESIGEN continuation
Gastrointestinal disorders	Less frequent	Lymphocytic colitis
Hepatobiliary disorders	Less frequent	Hepatitis, cytolytic hepatitis

Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Skin reactions (rash, maculo-papular, polymorphe erythema, pruritus, face oedema), DRESS syndrome, Stevens- Johnson syndrome, generalized exfoliative dermatitis Leukocytoclastic vasculitis
Reproductive system and breast disorders	Less frequent	Metrorrhagia in women taking oral contraceptives

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Risk of somnolence.

Management of overdose:

Symptomatic treatment will be implemented 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

Mechanism of action

Etifoxine hydrochloride belongs to the class of benzoxazine chemicals.

As antianxiety medicine, 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 GABAA receptor by an allosteric modulation, etifoxine binds preferentially to sub-units β2 and β3; studies show that etifoxine binds to a GABAA 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 GABAA 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Fumaric acid

Lactose monohydrate

Stearic acid

Capsule shell

Azorubine (Carmosine) (E122)

Gelatin

Patent blue V (E131)

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove the blister from the outer carton until required for use.

6.5 Nature and contents of container

60’s pack: Clear PVC/PVDC- aluminum blisters packed into a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

A59/2.6/0102

9. DATE OF FIRST AUTHORISATION

25 November 2025