Professional Information for KALMEXAN

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

KALMEXAN 50 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg etifoxine hydrochloride.

Excipients with known effect:

Contains sugar.

Each capsule contains 110 mg lactose monohydrate (see section 4.4).

Contains azorubine (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

Hard gelatine capsule, with a white-coloured opaque body and blue-coloured opaque cap containing an off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psychosomatic manifestations of anxiety.

4.2 Posology and method of administration

Posology

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.

Method of administration

For oral use.

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 KALMEXAN.
- Patients who have had severe dermatological reactions, including DRESS syndrome, Stevens-Johnson syndrome (SJS) and dermatitis exfoliative generalised, during previous treatment with KALMEXAN (see section 4.4).

4.4 Special warnings and precautions for use

Severe dermatological reactions:

Severe dermatological reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens-Johnson Syndrome (SJS) and generalised exfoliative dermatitis have been reported with KALMEXAN. The onset of skin toxicity with KALMEXAN usually ranged from a few days to 1 month, depending on the reactions. As per post-marketing data, outcome of skin reactions is mostly favourable after KALMEXAN withdrawal. No fatal outcome due to severe cutaneous adverse reactions has been reported with KALMEXAN. 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 KALMEXAN, the medicine should be immediately discontinued and never reintroduced (see section 4.3).

Severe hepatic reactions:

Severe cases of cytolytic hepatitis have been reported with the use of KALMEXAN during post-marketing experience. As per post-marketing data, time to onset of hepatic reactions after KALMEXAN introduction mainly occurred between 2 weeks and 1 month 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 KALMEXAN and around 1 month after treatment initiation. After the occurrence of liver toxicity with KALMEXAN, the medicine should be immediately discontinued and never reintroduced.

Lymphocystis colitis:

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

Metrorrhagia:

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

Central nervous system depressants:

Caution is advised when KALMEXAN is used in conjunction with central nervous system depressants.

Simultaneous intake of alcoholic drinks is not advised (see section 4.5).

Colourants:

KALMEXAN contains azorubine which is an azo colourant, which may cause allergic reactions.

Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take KALMEXAN.

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 considered:

Other central nervous system 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 KALMEXAN 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

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

KALMEXAN 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 KALMEXAN 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 KALMEXAN.

4.8 Undesirable effects

System organ class	Less frequent	Frequency unknown
Immune system disorders	Allergic reactions (urticaria, Quincke's oedema)	Anaphylactic shock
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	Rash maculo-papular, polymorphe erythema, pruritus, face oedema, DRESS syndrome, Stevens-Johnson syndrome, generalised exfoliative dermatitis	Leukocytoclastic vasculitis
Reproductive system	Metrorrhagia in women treated with oral	

and breast disorders	contraceptives.	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of KALMEXAN is important. It allows continued monitoring of the benefit/risk balance of [PRODUCT NAME]. Health care providers 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.

4.9 Overdose

See section 4.8. Treatment is symptomatic.

There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6 Tranquillisers.

Pharmacotherapeutic group: Nervous system, other anxiolytics.

ATC code: N05BX03.

Etifoxine 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 $GABA_A$ 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 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 crosses the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fumaric acid

Lactose monohydrate

Stearic acid.

Capsule composition (body and cap):

Patent blue V (E131)

Azorubine (E122)

Titanium dioxide (E171)

Gelatine.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC aluminium blister strips packed in a cardboard carton.

Pack size: 60 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

59/2.6/0167

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

14 July 2026

10. DATE OF REVISION OF THE TEXT