

Approved Professional Information for Medicines for Human Use: FOXISTRES

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

FOXISTRES 50 mg Hard Gelatin Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains etifoxine hydrochloride 50 mg.

Contains sugar: lactose monohydrate.

Each hard gelatin capsule contains 110 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

FOXISTRES 50 mg hard gelatin capsules.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FOXISTRES is indicated for 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

FOXISTRES should be taken orally, with a little water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- states of shock
- severely impaired liver and/or renal function
- myasthenia gravis
- because of the presence of lactose, this medicine is contra-indicated in patients with galactosaemia, glucose and galactose malabsorption syndrome or lactase deficit.
- Patients who have had severe cases of hepatitis or cytolytic hepatitis, during previous treatment with etifoxine, as contained in FOXISTRES.
- Patients who have had severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with etifoxine, as contained in FOXISTRES.

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 FOXISTRES with a very rare frequency. The onset of skin toxicity with

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

Severe hepatic reactions

Severe cases of cytolytic hepatitis have been reported with the use of FOXISTRES during post-marketing experience with a very rare frequency. As per post-marketing data, time to onset of hepatic reactions after FOXISTRES 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 FOXISTRES and around one month after treatment initiation. After the occurrence of liver toxicity with FOXISTRES, the medicine should be immediately discontinued and never reintroduced.

Lymphocytis colitis

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

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FOXISTRES. In case of watery diarrhoea with FOXISTRES, the medicine should be immediately discontinued.

Metrorrhagia

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

Precautions for use

Due to the risk of mutual potentiation

- it should be prescribed with caution in combination with central nervous system (CNS) depressants
- the simultaneous consumption of alcoholic beverages is not recommended.

Excipients: lactose monohydrate

FOXISTRES contains lactose:

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

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

Alcohol

The sedative effects of these substances are increased with the consumption of alcohol. Reduced alertness can make driving or operating machinery dangerous.

Avoid alcoholic beverages and medicines containing alcohol.

Combinations to be considered with caution

Other CNS depressants

Morphine derivatives (analgesics, antitussives and substitution treatments), benzodiazepines, hypnotics, neuroleptics, sedating H₁ antihistamines, sedating antidepressants, central antihypertensives, baclofen and thalidomide.

The concurrent use of FOXISTRES and these medicines may lead to increased CNS depression. Reduced alertness may make driving or operating machinery dangerous.

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding

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

FOXISTRES crosses the placental barrier.

Fertility

No data on male and female fertility are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) reported during clinical trials and postmarket spontaneous reports with etifoxine.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Nervous system disorders		Slight drowsiness at the start of treatment, which gradually resolves spontaneously during the course of treatment	
Skin and subcutaneous tissue disorders		Skin rash: maculopapular rash, erythema multiforme, pruritus, facial oedema Allergic manifestations: urticaria, angioedema	Anaphylactic shock DRESS Stevens Johnson syndrome Vasculitis or serum sickness type reaction
Hepatic disorders			Liver disease: cytolytic hepatitis, hepatitis

Reproductive system and breast disorders			Inter-menstrual bleeding in women on oral contraceptives
Gastrointestinal disorders			Lymphocytic colitis

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 asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

Post-marketing surveillance is used to confirm or deny the safety of a medicine after it is used in the general population by large numbers of people who have a wide variety of medical conditions. Where possible, following the SAHPRA adverse event reporting, kindly also report any suspected ADRs; new or existing safety, quality or effectiveness concerns occurring as a result of the use of this medicine via email to medsafety@austell.co.za

4.9 Overdose

Risk of drowsiness. Symptomatic treatment should be instituted, if necessary.

There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.6 Tranquillizers

Pharmacotherapeutic group: Other anxiolytics

ATC Code: N05BX03

Etifoxine hydrochloride belongs to the class of benzoxazine chemicals. Anxiolytic.

Etifoxine hydrochloride exerts a regulatory action on the autonomic nervous system, antagonizes the behavioural, physiological and biochemical effects of anxiogenic stress without demonstrable dependence and a withdrawal syndrome.

In vitro and in vivo reported studies carried out in rats and mice have shown that the anxiolytic activity of etifoxine is exerted mainly by a dual (direct and indirect) mechanism of action on the GABAA receptor aimed at enhancing GABAergic transmission:

- direct action by positive allosteric modulation of GABAA receptors, binding preferentially to the $\beta 2$ or $\beta 3$ subunits; studies reportedly show that the etifoxine binding site on the GABAA receptor is different from that of benzodiazepines
- indirect action by increasing cerebral neurosteroid production (by activating the mitochondrial translocation protein), including allopregnanolone, and these neurosteroids are positive allosteric modulators of the GABAA receptor.

5.2 Pharmacokinetic properties

Absorption

Etifoxine hydrochloride is well absorbed.

Distribution

It does not bind to blood cells.

Etifoxine hydrochloride crosses the placental barrier.

Biotransformation

Plasma levels of etifoxine and of its active metabolite (D3417) have half-lives of about 2 hours and 20 to 30 hours, respectively.

Elimination

Elimination is mainly urinary, with little or no unchanged etifoxine being found in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Fumaric acid

Lactose monohydrate

Stearic acid

Capsule cap:

Azorubine (E122) (Carmoisine)

Gelatin Ph. Eur.

Patent blue V (E131)

Titanium dioxide Ph. Eur. (E171)

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Water Ph. Eur. (14,5 %) target moisture

Capsule body:

Gelatin Ph. Eur.

Titanium dioxide Ph. Eur. (E171)

Water Ph. Eur. (14,5 %) target moisture

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

6.5 Nature and contents of container

Foxistres hard gelatin capsules are packed in blister packs comprising of clear PVC/
PVdC as a forming material and aluminium foil as the lidding material.

Pack sizes of 30's, 60's, 90's and 100's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

53/2.6/0254

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2023

10. DATE OF REVISION OF THE TEXT