PROPOSED CLEAN PROFRESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF MEDICINE
CALMATRIN (Capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains: etifoxine hydrochloride 50 mg.

Contains sugar: lactose monohydrate 110 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules
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
CALMATRIN is indicated for:
- Psychosomatic manifestations of anxiety.

4.2 Posology and method of administration
Posology
Usual Dose:
Take 150 mg to 200 mg daily 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 administration.
The capsules are to be taken with a little water.
Do not crush or open the capsules.

4.3 Contraindications
- CALMATRIN is contraindicated in patients with known 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 CALMATRIN.
- Patients who have had severe dermatological reactions, including DRESS syndrome, Stevens Johnson Syndrome (SJS) and dermatitis exfoliative generalized, during previous treatment with CALMATRIN.

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 dermatitis exfoliative generalized, have been reported with etifoxine hydrochloride with a very rare frequency. The onset of skin toxicity with etifoxine hydrochloride 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 [etifoxine hydrochloride withdrawal. No fatal outcome due to severe cutaneous adverse reactions has been reported with etifoxine hydrochloride. 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 hydrochloride, the medicine should be immediately discontinued and never reintroduced.

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

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

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

Alcohol and other central nervous system depressants
Caution is advised when etifoxine hydrochloride is used in conjunction with central nervous system depressants. Simultaneous intake of alcoholic drinks is not advised.

Excipients
Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, or glucose- galactose malabsorption should not take this medicine.

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 CALMATRIN 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
Pregnancy
In the absence of sufficient clinical data, the administration of CALMATRIN during pregnancy is not recommended.

Breastfeeding
Breastfeeding is not recommended.

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 etifoxine hydrochloride as in CALMATRIN 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 CALMATRIN.

4.8 Undesirable effects
a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Nervous System disorders	*Less frequent*	Slight drowsiness, occurring at the start of treatment and disappearing spontaneously with its continuation.
Gastrointestinal disorders	*Less frequent*	Lymphocytic colitis.
Hepatobiliary disorders	*Less frequent*	Hepatitis, cytolytic hepatitis.
Skin and subcutaneous tissue disorders	*Less frequent*	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.
	Frequency unknown	Anaphylactic shock, leukocytoclastic vasculitis.
Reproductive system and breast disorders	*Less frequent*	Metrorrhagia in women treated with oral contraceptives.

b. 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who- umc.org) found on SAHPRA website.

4.9 Overdose
If an overdose is taken, symptomatic treatment should be implied. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and Class: 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 conducted 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
Filling
Fumaric acid
Lactose monohydrate
Stearic acid

Capsule cap
Patent blue V (E131)
Azorubine (E122)
Titanium dioxide (E171)
Water (14,5 %) (Target Moisture)
Gelatine

Capsule body
Titanium dioxide (E171)
Water (14, 5 %) (Target Moisture)
Gelatine

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 30 ºC.

6.5 Nature and contents of container
Blister packs comprising of clear PVC (250 µm) / PVdC (90 g/m^2) as a forming material and aluminium foil (25 µm) as the lidding material. The blisters are further packed, with a leaflet, in a cardboard box. The capsules are packed into blister pack sizes of 60 or 100 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd
3 Gwen Lane, 4th Floor, Sandton, 2031.
Contact No.: +27 (0)10 594 5610
PV Email Address: pv@trinitypharma.co.za

8 REGISTRATION NUMBER(S)
To be confirmed

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
To be confirmed

10 DATE OF REVISION OF THE TEXT