

Emeside 250 mg Capsules

Summary of Product Characteristics Updated 10-Dec-2021 | Chemidex Pharma Ltd

1. Name of the medicinal product

Emeside Capsules

Ethosuximide Essential Generics 250 mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 250 mg ethosuximide.

Excipient with known effect

Each capsule contains 0.60 mg sodium ethyl hydroxybenzoate, 0.60 mg sodium propyl hydroxybenzoate and traces of soya lecithin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsules.

The capsules are clear oval soft gelatin capsules.

4. Clinical particulars

4.1 Therapeutic indications

Ethosuximide 250 mg Capsules gives selective control of absence seizures (petit mal) even when complicated by grand mal.

It is also indicated for myoclonic seizures.

4.2 Posology and method of administration

Posology

Adults, the Elderly and paediatric population over 6 years

Start with a small dose – 500 mg daily with increments of 250 mg every five to seven days until control is achieved with 1000 - 1500 mg daily. Occasionally 2000 mg in divided doses may be necessary.

Paediatric population aged 0-6 years

Children aged 0-6 years old and those who are unable to swallow capsules should be given ethosuximide oral liquid.

Effective plasma levels of ethosuximide normally lie between 40 and 100 mcg per ml, but the clinical response should be the criteria for the regulation of the dosage. The half-life of ethosuximide in the plasma is more than 24 hours but the daily dose if large is more comfortably divided between morning and evening.

Currently available clinical trial data regarding the use of ethosuximide in the paediatric population are described in section 5.1.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to soya oil (see section 4.4).

Porphyrias.

4.4 Special warnings and precautions for use

General

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A

meta-analysis of randomised placebo controlled trials of anti-epileptic drugs (AEDs) has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for ethosuximide. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

All patients treated with AEDs should be routinely evaluated for depression and anxiety.

Ethosuximide, when used alone in mixed types of epilepsy, may increase the frequency of generalised tonic clonic (grand mal) seizures in some patients.

As with other anticonvulsants, it is important to proceed slowly when increasing or decreasing dosage, as well as when adding or eliminating other medication. Abrupt withdrawal of anticonvulsant medication may precipitate absence (petit mal) seizures.

Haemopoietic Effect

Special attention should be given to clinical symptoms of bone marrow damage (fever, angina, haemorrhage) (see section 4.8). It is recommended to check the blood count regularly (initially monthly, after one year every six months) to identify potential bone marrow damage. At a leucocyte count of less than 3500/mm³ or a granulocyte ratio of less than 25%, the dose should be reduced or the therapy discontinued. The liver enzymes should also be checked regularly.

Hepatic/Renal Impairment

Ethosuximide should be used with extreme caution in patients with impaired hepatic or renal function.

Periodic urinalysis and liver function studies are advised for all patients receiving the drug. Ethosuximide is capable of producing morphological and functional changes in the animal liver. In humans, abnormal liver and renal function studies have been reported.

Autoimmune Disorders

Cases of systemic lupus erythematosus have been reported with the use of ethosuximide. The physician should be alert to this possibility. Additionally, lupus-like reactions have been reported in children given ethosuximide. They vary in severity from systemic immunological disorders, which include the nephrotic syndrome, to the asymptomatic presence of antinuclear antibodies. The nephrotic syndrome is rare and a complete recovery has usually been reported on drug withdrawal.

Severe Cutaneous Adverse Reactions (SCARs)

Hypersensitivity Syndrome (HSS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including ethosuximide. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The interval between the first drug exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately.

Ethosuximide should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with ethosuximide or other anticonvulsant drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) have been reported with the use of ethosuximide. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS (see section 4.4), occurrence of rash and should be monitored closely for skin reactions. Patients should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, ethosuximide treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient

has developed SJS or TEN with the use of ethosuximide, ethosuximide must not be re-started in this patient at any time.

If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstatement of therapy, further ethosuximide medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to ethosuximide may be higher in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of human leukocyte antigen HLA-B*1502, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. HLA-B*1502 may be associated with increased risk of developing SJS/TEN in patients of Thai and Han Chinese ancestry taking drugs associated with SJS/TEN, including ethosuximide. If these patients are known to be positive for HLA-B*1502, the use of ethosuximide should only be considered if the benefits are thought to exceed the risks.

In the Caucasian and Japanese population, the frequency of HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

Information for Patients

Patients taking ethosuximide should be advised of the importance of adhering strictly to the prescribed dosage regimen.

Patients should be instructed to promptly contact their physician if they develop signs and/or symptoms (e.g. sore throat, fever) suggesting an infection.

Withdrawal

If ethosuximide is being substituted for another anti-epileptic drug the latter must not be withdrawn abruptly but the replacement made gradually with overlap of the preparations otherwise petit mal may break through.

Ethosuximide should always be withdrawn slowly.

Excipients

This medicinal product contains sodium ethyl hydroxybenzoate and sodium propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicinal product contains soya oil. Patients who are allergic to peanut or soya should not use this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

Since ethosuximide may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of these drugs may be necessary (e.g. ethosuximide may elevate phenytoin serum levels and valproic acid has been reported to both increase and decrease ethosuximide levels).

The plasma concentrations of ethosuximide may be reduced by carbamazepine, primidone, phenobarbitone and lamotrigine and increased by isoniazid.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ethosuximide crosses the placenta. Reports suggest an association between the use of other anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to those women. Cases of birth defects have been reported with ethosuximide. The prescribing physician should weigh the benefit versus risk of ethosuximide in treating or counselling epileptic women of childbearing potential.

Breastfeeding

Ethosuximide is excreted in breast milk. Because the effects of ethosuximide on the nursing infant are unknown, caution should be exercised when ethosuximide is administered to a nursing mother. Ethosuximide should be used in nursing mothers only if the benefits clearly outweigh the risks. Breast feeding is best avoided.

4.7 Effects on ability to drive and use machines

Ethosuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or other such activities requiring alertness. Therefore, the patient should be cautioned accordingly.

4.8 Undesirable effects

Frequencies reported are as follows:

† Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Not known (cannot be estimated from the available data)

* AE frequency estimated from post-marketing safety database

| MedDRA System Organ Class | Frequency† | Undesirable Effects |
|--|-------------------|---|
| Blood and lymphatic system disorders | Uncommon | Agranulocytosis*, Aplastic anaemia*, Eosinophilia*, Leukopenia*, Pancytopenia*, Bone marrow failure |
| | Not Known | Thrombocytopenia |
| Immune system disorders | Uncommon | Hypersensitivity* |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| Psychiatric disorders | Uncommon | Aggression*, Sleep terror*, Depression*, Suicidal ideation*, Psychotic disorder*, Sleep disorder* |
| | Not known | Euphoric mood, Apathy, Libido increased |
| Nervous system disorders | Common | Headache, Ataxia, Dizziness, Somnolence |
| | Uncommon | Psychomotor hyperactivity*, Lethargy, Disturbance in attention* |
| | Not Known | Extrapyramidal side effects, Increased frequency of grand mal convulsions |
| Eye disorders | Uncommon | Myopia* |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Hiccups |
| Gastrointestinal disorders | Common | Abdominal pain, Abdominal pain upper, Gastrointestinal disorder, Nausea, Abdominal discomfort, Vomiting |
| | Uncommon | Diarrhoea, Gingival hypertrophy*, Swollen tongue* |
| Skin and subcutaneous tissue disorders | Common | Rash erythematous, Urticaria |
| | Uncommon | Stevens-Johnson syndrome* |
| | Not Known | Drug reaction with eosinophilia and systemic symptoms (DRESS) |
| Musculoskeletal and connective tissue disorders | Uncommon | Systemic lupus erythematosus* |
| Renal and urinary disorders | Uncommon | Haematuria* |
| Reproductive system and breast disorders | Uncommon | Vaginal haemorrhage* |
| General disorders and administration site conditions | Uncommon | Fatigue, Irritability* |
| Investigations | Uncommon | Weight decreased |

Summary of safety profile

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with ethosuximide treatment (see section 4.4).

Psychiatric or psychological aberrations associated with ethosuximide administration may be noted particularly in patients who have previously exhibited psychological abnormalities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdoses may produce nausea, vomiting and CNS depression including coma with respiratory depression. A relationship between ethosuximide toxicity and its plasma levels has not been established.

If less than 2 g have been taken, fluids should be given by mouth. If a larger dose has been taken the stomach should be emptied, respiration maintained and any other symptoms treated accordingly. Activated charcoal and purgatives are known to be used in the treatment of overdosage. Haemodialysis may be useful. Forced diuresis and exchange transfusions are ineffective.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Succinimide derivates, ATC code: N03AD01

Mechanism of action

The reduction of seizure frequency is thought to be achieved by depression of the motor cortex and elevation of the threshold to convulsive stimuli as seen by the suppression of the characteristic spike and wave EEG pattern.

Pharmacodynamic effects

Ethosuximide gives selective control of absence seizures (petit mal) even when complicated by grand mal. It is also indicated for myoclonic seizures. Compared to other anti-convulsants, ethosuximide is more specific for pure petit mal.

Paediatric population

In a double-blind randomized trial of 20 weeks duration in 453 children aged 2.5 to 13 years old with newly diagnosed childhood absence epilepsy, the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid and lamotrigine as monotherapy in childhood absence epilepsy were investigated. Those treated with either ethosuximide or valproic acid had higher freedom-from-failure rates (53% and 58%, respectively) than those given lamotrigine (29%; odds ratio with ethosuximide vs. lamotrigine, 2.66; 95% confidence interval [CI], 1.65 to 4.28; odds ratio with valproic acid vs. lamotrigine, 3.34; 95% CI, 2.06 to 5.42; $P < 0.001$ for both comparisons). In both prespecified and post hoc analyses, ethosuximide resulted in fewer attentional effects as compared with valproic acid (at week 16 and week 20, the percentage of subjects with a Confidence Index score of 0.60 or higher in the Conners' Continuous Performance Test was greater in the valproic acid group than in the ethosuximide group (49% vs. 33%; odds ratio, 1.95; 95% CI, 1.12 to 3.41; $P = 0.03$) and the lamotrigine group (49% vs. 24%; odds ratio, 3.04; 95% CI, 1.69 to 5.49; $P < 0.001$).

5.2 Pharmacokinetic properties

Absorption

Ethosuximide is readily absorbed from the gastro-intestinal tract and extensively metabolised in the liver.

Distribution

It is widely distributed throughout the body but is not significantly bound to plasma proteins, so saliva concentrations may be useful for monitoring.

Peak serum levels occur 1 to 7 hours after single oral dose. Therapeutic levels are between 40 and 100 mcg/ml. It has a long elimination half life: adults 40 - 60 hours; children 30 hours.

Elimination

It is excreted in the urine mainly in the form of its metabolites.

5.3 Preclinical safety data

The results of the preclinical tests do not add anything of further significance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Macrogol 400

Gelatin

Glycerin

Sodium ethyl hydroxybenzoate (E 215)

Sodium propyl hydroxybenzoate (E 217)

Miglycol 812 (Fractionated coconut oil)

Soya lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30°C away from moisture. Do not refrigerate.

Keep out of sight and reach of children.

6.5 Nature and contents of container

Grey polypropylene container with a white low density polyethylene cap containing 56, 112 or 500 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Chemidex Pharma Ltd.

T/S Essential Generics

7 Egham Business Village,

Crabtree Road, Egham, Surrey

TW20 8RB

United Kingdom

8. Marketing authorisation number(s)

PL 17736/0085

9. Date of first authorisation/renewal of the authorisation

29/01/2007

10. Date of revision of the text

02/12/2021

Company Contact Details

Chemidex Pharma Ltd

Address

7 Egham Business Village, Crabtree Road, Egham,
Surrey, TW20 8 RB, UK

Telephone

+44 (0)1784 477 167

Medical Information Direct Line

+44 (0)1784 477167

WWW

<http://www.chemidex.co.uk>

Fax

+44 (0)1784 471 776

Medical Information e-mail

info@chemidex.co.uk info@essentialpharmaceuticals