
NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZARONTIN 250 mg capsules

ZARONTIN SYRUP 250 mg/5mL syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of ethosuximide.

Each 5 mL of syrup contains 250 mg of ethosuximide

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

ZARONTIN capsules: Clear, medium orange printed with P-D 237

ZARONTIN SYRUP: Clear, yellow to pink solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZARONTIN is indicated for the control of petit mal epilepsy.

4.2 Dosage and Method of Administration

Dose

Recommended initial daily dose for children and adults is approximately 20-30 mg/kg administered in two divided doses. This regimen will frequently achieve plasma levels in the therapeutic range of 40-100 mg/L (optimum 75 mg/L). As the dose serum level relationship may be curvilinear in individual patients dosage should be increased by small increments.

One useful method is to increase the daily dose by 250 mg every four to seven days until control is achieved with minimal side effects. Dosages exceeding 1.5 g daily, in divided doses should be administered only under the strictest supervision of the physician. Plasma level monitoring is recommended. ZARONTIN may be administered in combination with other anticonvulsants when other forms of epilepsy coexist with petit mal.

Method of Administration

ZARONTIN is administered orally.

4.3 Contraindications

Ethosuximide is contraindicated in patients with hypersensitivity to succinimides, ethosuximide or any components of this medication.

4.4 Special Warnings and Precautions for Use

General

Ethosuximide, when used alone in mixed types of epilepsy, may increase the frequency of 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 petit mal status.

Haematopoietic Effect

Blood dyscrasias, including some with fatal outcome, have been reported to be associated with the use of ethosuximide, therefore, periodic blood counts should be performed. Should signs and/or symptoms of infection (e.g. sore throat, fever) develop, blood count determinations should be considered at that point.

Hepatic/Renal Impairment

Ethosuximide is capable of producing morphological and functional changes in the animal liver. In humans, abnormal liver and renal function studies have been reported. Ethosuximide should be administered with extreme caution to patients with known liver or renal disease. Periodic urinalysis and liver function studies are advised for all patients receiving the drug.

Autoimmune Disorders

Cases of systemic lupus erythematosus have been reported with the use of ethosuximide. The physician should be alert to this possibility.

Serious Dermatologic Reactions

Serious dermatologic reactions, including Stevens-Johnson syndrome (SJS), have been reported with ethosuximide treatment. SJS can be fatal. The onset of symptoms is usually within 28 days, but can occur later. Upon the appearance of a rash for which an alternative aetiology cannot be defined, ethosuximide should be discontinued.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ethosuximide exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy; and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. DRESS is sometimes fatal. Discontinue ethosuximide if DRESS is suspected.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including ethosuximide, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of

suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing ethosuximide or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Information for Patients

Ethosuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a motor vehicle or other such activity requiring alertness; therefore, the patient should be cautioned accordingly.

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.

4.5 Interactions with Other Medicines 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).

4.6 Fertility Pregnancy and Lactation

Use in Pregnancy - Category D

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;

Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Ethosuximide crosses the placenta. The risk of a mother with epilepsy giving birth to a baby with birth defects is about three times that of the general population. Some of this risk is due to the anticonvulsant drugs taken. Cases of birth defects have been reported with ethosuximide. Mothers taking more than one anticonvulsant drug might have a higher risk of having a baby with a malformation than mothers taking one drug.

Use in Lactation

Ethosuximide is excreted in human 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.

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, using machinery or other such activity requiring alertness.

4.8 Undesirable Effects

Blood and lymphatic system disorders: agranulocytosis, aplastic anaemia, eosinophilia, leucopenia, pancytopenia, bone marrow failure.

Immune system disorders: hypersensitivity.

Metabolism and nutrition disorders: decreased appetite.

Psychiatric disorders: aggression, euphoric mood, sleep terror, libido increased, increased state of depression, overt suicidal ideation, psychotic disorder, paranoid psychosis, disturbances of sleep, night terrors, inability to concentrate and sleep disorder.

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

Nervous system disorders: drowsiness, dizziness, headache, ataxia, somnolence, psychomotor hyperactivity, hyperactivity, lethargy, disturbances in attention.

Eye disorders: myopia.

Respiratory, thoracic and mediastinal disorders: hiccups.

Gastrointestinal disorders: epigastric and abdominal pain, abdominal pain upper, anorexia, gastrointestinal disorder, diarrhoea, nausea, abdominal discomfort, vomiting, gingival hypertrophy, swollen tongue, vague gastric upset, cramps.

Skin and subcutaneous tissue disorders: drug reaction with eosinophilia and systemic symptoms, rash erythematous, Stevens-Johnson syndrome, urticaria, hirsutism.

Musculoskeletal and connective tissue disorders: systemic lupus erythematosus.

Renal and urinary disorders: haematuria.

Reproductive system and breast disorders: vaginal haemorrhage.

General disorders and administration site conditions: fatigue, irritability.

Investigations: weight decreased.

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 <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

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. The therapeutic range is 40 mcg/mL to 100 mcg/mL, although levels as high as 150 mcg/mL have been reported without signs of toxicity.

Treatment

Treatment is symptomatic and supportive of respiratory and cardiovascular functions. There is no specific antidote available. Activated charcoal may be used to reduce drug absorption and is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Haemodialysis may be useful, but forced diuresis and exchange transfusions are ineffective.

Ipecac-induced emesis is not recommended because of the potential for CNS depression.

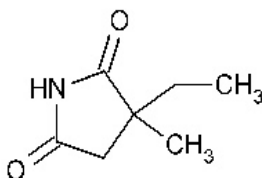
Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiepileptics, succinimide derivatives, ATC code: N03AD01

ZARONTIN contains the active component ethosuximide.



CAS number: 77-67-8.

Ethosuximide is chemically described as α -ethyl- α -methylsuccinimide with an empirical formula of $C_7H_{11}NO_2$ and a molecular weight of 141.17. The molecular structure of ethosuximide is shown above. It is a white or almost white powder or waxy solid, freely soluble in water, very soluble in alcohol, in ether and in methylene chloride.

Ethosuximide suppresses the paroxysmal spike and wave pattern, which is common in petit mal seizures. The frequency of epileptiform attacks is reduced, apparently by depression of the motor cortex and elevation of the threshold of the central nervous system to convulsive stimuli.

5.2 Pharmacokinetic Properties

No information

5.3 Preclinical Safety Data

No information

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

ZARONTIN capsules also contains gelatin, glycerol, macrogol 400, sorbitol, erythrosine CI45430, quinoline yellow CI47005 and Opacode WB monogramming ink.

ZARONTIN SYRUP also contains sodium benzoate 2.38 mg/mL as preservative, sucrose 60% w/v, glycerol 12.5% w/v. Other excipients are saccharin sodium, sodium citrate, citric acid monohydrate, raspberry flavour and purified water.

6.2 Incompatibilities

Ethosuximide may interact with concurrently administered antiepileptic drugs. Refer to section 4.5

6.3 Shelf Life

ZARONTIN capsules: 2 years

ZARONTIN SYRUP: 3 years

6.4 Special Precautions for Storage

ZARONTIN capsules: Store below 30°C.

ZARONTIN SYRUP: Store below 25°C.

6.5 Nature and Contents of Container

ZARONTIN capsules: HDPE bottles of 100 or 200.

ZARONTIN SYRUP: glass bottles of 200 mL.

6.6 Special Precautions for Disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

New Zealand

Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

27 February 2017