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# AUSTRALIAN PRODUCT INFORMATION – ZARONTIN (ETHOSUXIMIDE) CAPSULES AND SYRUP

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## 1 NAME OF THE MEDICINE

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Ethosuximide

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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ZARONTIN contains the active component ethosuximide.

Each ZARONTIN capsule contains 250 mg ethosuximide. ZARONTIN syrup contains ethosuximide 250 mg/5mL.

Excipients with known effect:

ZARONTIN syrup contains benzoates, saccharin and sugars.

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

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ZARONTIN Capsules: Clear medium orange capsules printed P-D 237.

ZARONTIN Syrup: A clear slightly yellowish to slightly pinkish liquid.

## 4 CLINICAL PARTICULARS

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### 4.1 Therapeutic indications

ZARONTIN is indicated for the control of petit mal epilepsy.

### 4.2 Dose and method of administration

ZARONTIN is administered orally.

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.

### 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.

### ***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 Reaction***

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 (See Section 5.1 Pharmacodynamic Properties, Clinical trials).

### ***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.

### ***Use in Hepatic Impairment***

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

### ***Use in Renal Impairment***

In humans, renal function studies have been reported. Ethosuximide should be administered with extreme caution to patients with known renal disease. Periodic urinalysis are advised for all patients receiving the drug.

### ***Use in the elderly***

No data available.

### ***Paediatric use***

Refer to Section 4.2 Dose and Method of Administration.

### ***Effects on laboratory tests***

No data available

## **4.5 Interactions with other medicines and other forms of interactions**

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**

### ***Effects on fertility***

No data available.

### ***Use in pregnancy – 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. Cases of birth defects have been reported with ethosuximide.

### ***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 Adverse effects (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 suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

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### **5.1 Pharmacodynamic properties**

#### **Mechanism of action**

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.

#### **Clinical trials**

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.

## 5.2 Pharmacokinetic properties

No data available.

## 5.3 Preclinical safety data

### **Genotoxicity**

No data available.

### **Carcinogenicity**

No data available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### **Capsule**

It also contains gelatin, glycerol, macrogol 400, Sorbitol Special Polyol (ARTG PI No: 3876), erythrosine, quinoline yellow and Opacode WB water based Monogramming Ink NSP-78-18022 White (ARTG PI No: 3883)

## **Syrup**

It also contains sodium benzoate (2.38 mg/mL as a preservative), sucrose (60 mg/mL), glycerol (12.5 mg/mL), saccharin sodium, sodium citrate dihydrate, citric acid monohydrate, Raspberry Flavour 23 P 082 (ARTG PI No: 4501) and purified water

## **6.2 Incompatibilities**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## **6.3 Shelf life**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## **6.4 Special precautions for storage**

### **Capsule**

Store below 30°C.

### **Syrup**

Store below 25°C.

## **6.5 Nature and contents of container**

### **Capsule**

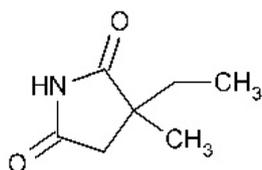
HDPE bottles of 100 capsules or 200 capsules with PP child resistant closure.

### **Syrup**

Glass bottles of 200 mL with PP child resistant closure.

## **6.6 Physicochemical properties**

### **Chemical structure**



Ethosuximide is chemically described as  $\alpha$ -ethyl- $\alpha$ -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.

Ethosuximide is a white or almost white powder or waxy solid, freely soluble in water, very soluble in alcohol, in ether and in methylene chloride.

### **CAS number:**

77-67-8

## **7 MEDICINE SCHEDULE (POISONS STANDARD)**

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Schedule 4 – Prescription only Medicine

## **8 SPONSOR**

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Clinect Pty Ltd

120-132 Atlantic Drive

Keysborough VIC 3173

Australia

Free Call Australia:

1800 899 005

## 9 DATE OF FIRST APPROVAL

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Capsules: 29 April 2003.

Syrup: 27 June 2002.

## 10 DATE OF REVISION

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13 January 2022

### Summary table of changes

Section Changed	Summary of new information
All	PI reformat and minor editorial changes