Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zarontin 250mg/5ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 250 mg ethosuximide.

Excipients with known effect:
Each 5 ml contains 3 g sucrose, 5 mg glucose , 12 mg sodium benzoate (E211) and 42 mg propylene glycol (E1520).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

A clear, slightly yellowish to slightly pinkish, dye-free, raspberry flavoured syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primarily useful in absence seizures. When generalised tonic clonic seizures (grand mal) and other forms of epilepsy co-exist with absence seizures, Zarontin may be administered in combination with other antiepileptic drugs.

4.2 Posology and method of administration

Posology

Adults, the Elderly and paediatric population over 6 years
Start with a small dose – 500 mg (10ml) 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
Begin with a daily dose of 250 mg (5 ml) and increase the dose gradually by small increments every few days until control is achieved. The optimal dose in most children is 20 mg/kg/day. The maximum dose should be 1000 mg.

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.
The pack contains a measuring cup graduated from 2 ml to 15 ml to adjust the doses

4.3 Contraindications

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

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 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/mm^3 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
Zarontin 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 Zarontin Syrup. 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, Zarontin Syrup 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 Zarontin Syrup, Zarontin Syrup 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 reinstitution 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.

Excipients

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase should not take this medicine. May be harmful to teeth.

Glucose
Patients with rare glucose-galactose malabsorption should not take this medicine.

Sodium benzoate (E211)
This medicine contains 12 mg sodium benzoate (E211) in each 5 ml syrup which is equivalent to 2.4 mg/ml. Sodium benzoate (E211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). Increase of bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

Propylene glycol (E1520)
This medicine contains 42 mg propylene glycol (E1520) in each 5 ml syrup which is equivalent to 8.4 mg/ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 5 ml syrup, this 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).

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.

Breast-feeding
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 (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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 erythematous*
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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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 2g 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 derivatives, ATC code: N03AD01

Ethosuximide is an anticonvulsant.

Ethosuximide suppresses the paroxysmal spike and wave pattern common to absence (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. Compared with other succinimide anticonvulsants, ethosuximide is more specific for pure absence seizures.

In a double-blind, randomized trial of 20 week 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

Ethosuximide is given by mouth. It is completely and rapidly absorbed from the gastrointestinal tract. Peak serum levels occur 1 to 7 hours after a single oral dose. Ethosuximide is not significantly bound to plasma proteins and therefore the drug is present in saliva and CSF in concentrations that approximate to that of the plasma. Therapeutic concentrations are in the range of 40 to 100 micrograms/ml. Ethosuximide is extensively metabolised to at least 3 plasma metabolites. Only between 12% and 20% of the drug is excreted unchanged in the urine. The elimination half life of ethosuximide is long, 40 to 60 hours in adults and 30 hours in children.

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

Sodium citrate
Sodium benzoate (E211)
Saccharin sodium
Sucrose
Glycerol
Raspberry flavour including glucose and propylene glycol (E1520)
Citric acid monohydrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

200 ml amber glass bottle with a child-resistant cap and a polypropylene measuring cup graduated from 2 ml to 15 ml.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Essential Pharma (M) Limited
Vision Exchange Building
Triq it-Territorjals, Zone 1
Central Business District
Birkirkara, CBD 1070
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8 MARKETING AUTHORISATION NUMBER

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