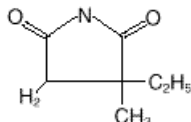


## Zarontin® (Ethosuximide Capsules, USP)

### DESCRIPTION

Zarontin (ethosuximide) is an anticonvulsant succinimide, chemically designated as alpha-ethyl-alpha-methyl-succinimide, with the following structural formula:



Each Zarontin capsule contains 250 mg ethosuximide, USP. Also contains: polyethylene glycol 400, NF. The capsule contains D&C yellow No. 10; FD&C red No. 3; gelatin, NF; glycerin, USP; and sorbitol.

### CLINICAL PHARMACOLOGY

Ethosuximide suppresses the paroxysmal three cycle per second spike and wave activity associated with lapses of consciousness which is common in 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.

### INDICATIONS AND USAGE

Zarontin is indicated for the control of absence (petit mal) epilepsy.

### CONTRAINDICATION

Ethosuximide should not be used in patients with a history of hypersensitivity to succinimides.

### WARNINGS

#### Blood dyscrasias

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 (eg, sore throat, fever) develop, blood counts should be considered at that point.

#### Effects on Liver and Kidneys

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.

#### Systemic Lupus Erythematosus

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

#### Suicidal Behavior and Ideation:

Antiepileptic drugs (AEDs), including Zarontin, increase the risk of suicidal thoughts or behavior 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 behavior, and/or any unusual changes in mood or behavior.

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 behavior compared to patients randomized to

placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior 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 behavior 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 behavior 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 behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. 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 analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

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 behavior 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 Zaronitin or any other AED must balance the risk of suicidal thoughts and behavior 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 behavior. Should suicidal thoughts and behavior 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 behavior 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 behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

**Usage in Pregnancy:**

Ethosuximide crosses the placenta.

Reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less

systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

Cases of birth defects have been reported with ethosuximide. The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, eg. genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

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.

## **PRECAUTIONS**

### **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 absence (petit mal) status.

### **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 (eg, sore throat, fever), suggesting an infection.

Patients, their caregivers, and families should be counseled that AEDs, including Zarontin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: Pregnancy section).

### **Drug Interactions:**

Since Zarontin (ethosuximide) may interact with concurrently administered antiepileptic drugs, periodic

serum level determinations of these drugs may be necessary (eg, ethosuximide may elevate phenytoin serum levels and valproic acid has been reported to both increase and decrease ethosuximide levels).

**Pregnancy:**

To provide information regarding the effects of in utero exposure to Zarontin, physicians are advised to recommend that pregnant patients taking Zarontin enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website: <http://www.aedpregnancyregistry.org/>

See WARNINGS.

**Pediatric Use:**

Safety and effectiveness in pediatric patients below the age of 3 years have not been established. (See DOSAGE AND ADMINISTRATION section.)

**ADVERSE REACTIONS**

**Body As A Whole:** Allergic reaction.

**Gastrointestinal System:** Gastrointestinal symptoms occur frequently and include anorexia, vague gastric upset, nausea and vomiting, cramps, epigastric and abdominal pain, weight loss, and diarrhea. There have been reports of gum hypertrophy and swelling of the tongue.

**Hemopoietic System:** Hemopoietic complications associated with the administration of ethosuximide have included leukopenia, agranulocytosis, pancytopenia, with or without bone marrow suppression, and eosinophilia.

**Nervous System:** Neurologic and sensory reactions reported during therapy with ethosuximide have included drowsiness, headache, dizziness, euphoria, hiccups, irritability, hyperactivity, lethargy, fatigue, and ataxia. Psychiatric or psychological aberrations associated with ethosuximide administration have included disturbances of sleep, night terrors, inability to concentrate, and aggressiveness. These effects may be noted particularly in patients who have previously exhibited psychological abnormalities. There have been rare reports of paranoid psychosis, increased libido, and increased state of depression with overt suicidal intentions.

**Integumentary System:** Dermatologic manifestations which have occurred with the administration of ethosuximide have included urticaria, Stevens-Johnson syndrome, systemic lupus erythematosus, pruritic erythematous rashes, and hirsutism.

**Special Senses:** Myopia.

**Genitourinary System:** Vaginal bleeding, microscopic hematuria.

**OVERDOSAGE**

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 of serum levels 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 should include emesis (unless the patient is or could rapidly become obtunded, comatose, or convulsing) or gastric lavage, activated charcoal, cathartics, and general supportive measures. Hemodialysis may be useful to treat ethosuximide overdose. Forced diuresis and exchange transfusions are ineffective.

**DOSAGE AND ADMINISTRATION**

Zarontin is administered by the oral route. The *initial* dose for patients 3 to 6 years of age is one capsule (250 mg) per day; for patients 6 years of age and older, 2 capsules (500 mg) per day. The dose thereafter must be individualized according to the patient's response. 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. The *optimal* dose for most pediatric patients is 20 mg/kg/day. This dose has given average plasma levels within the accepted therapeutic range of 40 to 100 mcg/mL. Subsequent dose schedules can be based on effectiveness and plasma level determinations.

Zarontin may be administered in combination with other anticonvulsants when other forms of epilepsy coexist with absence (petit mal). The *optimal* dose for most pediatric patients is 20mg/kg/day.

## HOW SUPPLIED

### Zarontin is supplied as:

N 0071-0237-24—Bottles of 100. Each capsule contains 250 mg ethosuximide.

Store at 25 ° C (77 ° F); excursions permitted to 15-30 ° C (59-86 ° F) [see USP Controlled Room Temperature].

Rx only



LAB-0094-5.0

Revised April 2009