

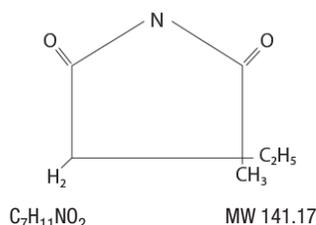
Ethosuximide Oral Solution, USP

250 mg/5 mL

Rx only

DESCRIPTION

Ethosuximide is an anticonvulsant succinimide, chemically designated as alpha-ethyl-alpha-methyl-succinimide, with the following structural formula:



Each teaspoonful (5 mL), for oral administration, contains 250 mg ethosuximide, USP. Also contains artificial raspberry flavor, citric acid, ethyl maltol, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, purified water, saccharin sodium, sodium benzoate, sodium citrate, and sucrose.

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

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

CONTRAINDICATIONS

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 (e.g., 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 ethosuximide, 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: 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 ethosuximide 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.

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. Ethosuximide should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS, use of this drug should not be resumed and alternative therapy should be considered.

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 methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., 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

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking ethosuximide. Instruct patients to take ethosuximide only as prescribed.

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 when they develop signs and/or symptoms suggesting an infection (e.g., sore throat, fever).

Patients, their caregivers, and families should be counseled that AEDs, including ethosuximide, 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.

Prior to initiation of treatment with ethosuximide, the patient should be instructed that a rash may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

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 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).

Pregnancy

To provide information regarding the effects of *in utero* exposure to ethosuximide, physicians are advised to recommend that pregnant patients taking ethosuximide 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. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

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, 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

Ethosuximide is administered by the oral route. The *initial* dose for patients 3 to 6 years of age is one teaspoonful (250 mg) per day; for patients 6 years of age and older, 2 teaspoonfuls (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.

Ethosuximide 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 20 mg/kg/day.

HOW SUPPLIED

Ethosuximide oral solution, USP 250 mg/5 mL is supplied in bottles of 16 fl. oz. NDC 61748-024-16. Each 5 mL of oral solution contains 250 mg ethosuximide in a raspberry flavored base. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from freezing and light.

Dispense in a tight, light-resistant container with a child-resistant closure.

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