ETHOSUXIMIDE - ethosuximide capsule
Zydus Pharmaceuticals (USA) Inc.

Ethosuximide Capsules, USP

DESCRIPTION

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

Each ethosuximide capsule intended for oral administration contains 250 mg of ethosuximide, USP and contains the following inactive ingredients: FD&C red 40 aluminum lake, FD&C yellow 6 aluminum lake, gelatin, glycerin, light mineral oil, methyl paraben, polyethylene glycol, propyl paraben, and sorbic acid. The capsule shell is composed of white imprinting ink containing cepacide white S-1-7678 as colorant which contains the following inactive ingredients: ammonium hydroxide, isopropyl alcohol, w-5-hexyl acetate, propylene glycol, shellac glaze, stearic acid and titanium dioxide.

CLINICAL PHARMACOLOGY

Ethosuximide suppresses the paroxysmal after discharge per second spike and wave activity associated with lapses of consciousness which is common in absence (petit mal) seizures. The frequency of epileptiform activity is reduced, apparently by depression of the ionic currents and stabilization of the threshold of the central nervous system to convulsive stimuli.

INDICATIONS AND USAGE

Ethosuximide capsule 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 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 any unusual changes in mood or behavior, including abrupt changes in behavior.

Serious Dermatologic Reactions

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

Usage in Pregnancy

Ethosuximide crosses the placenta.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

<table>
<thead>
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<th>Indication Placebo Patients</th>
<th>Events</th>
<th>Drug Patients</th>
<th>Events</th>
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<th>Incidence in Drug Patients</th>
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<td>1.9</td>
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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.

Amore considering prescribing ethosuximide or any other AED must balance the risk of suicidal thoughts and behavior with the risks 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 or behavior. Should suicidal thoughts and behaviors 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 or behavior and should be advised of the need to be alert for the emergence or worsening of the symptoms and to report 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. Stevens-Johnson syndrome (SJS) can be fatal. The onset of symptoms is usually within 28 days, but can occur later. Ethosuximide should be discontinued as soon as the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest Stevens-Johnson syndrome (SJS), use of this drug should not be resumed and alternative therapy should be considered.

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Table 1 shows absolute and relative risk by indication for all evaluated AEDs.
Ethosuximide capsules are 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 strict 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 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.

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. Acute overdoses may result in respiratory depression with metabolic acidosis, seizures, hypothermia, and coma. An electrocardiogram should be performed. Treatment should include emesis (unless the patient is or could rapidly become obtunded, comatose, or unresponsive), activated charcoal, cathartics, and general supportive measures. Treatment includes the use of intravenous fluids and oxygen, if necessary. Treatment of respiratory depression should include the use of respiratory support, such as intermittent positive pressure ventilation.

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 an anticonvulsant medication may precipitate seizures (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 not responding may be advised of the importance of adhering strictly to the prescribed dosage regimen.

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 DOSAGE AND ADMINISTRATION section).

Drug Interactions
Since ethosuximide may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of these drugs may be necessary. For example, ethosuximide may elevate phenytoin serum levels. Total serum protein and serum albumin determinations should be performed. Levels as high as 150 mcg/mL have been reported without signs of toxicity.

Pregnancy
To provide information regarding the effects of intrauterine 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 WARNING).

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 gastritis/peptic ulcer and swelling of the tongue.

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

Hepatic System:
Neurologic and sensory reactions reported during therapy with ethosuximide have included drowsiness, headache, dizziness, euphoria, hiccup, vertigo, hyporeflexia, lethargy, fatigue, and anemia. Psychiatric or psychological aberrations associated with ethosuximide administration have included disturbances of sleep, nightmares, inability to concentrate, and aggressiveness. These effects may be mild particularly inpatients who have previously exhibited psychological abnormalities. There have been 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.

Gastrointestinal System:
Vaginal bleeding, microscopic hematuria.

OVERDOSAGE
Acute overdosage 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 unresponsive) or gastric lavage, activated charcoal, cathartics, and general supportive measures. Treatment includes the use of intravenous fluids and oxygen, if necessary. Treatment of respiratory depression should include the use of respiratory support, such as intermittent positive pressure ventilation.

Dosage and Administration
Ethosuximide capsules are 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 strict 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 Capsules USP, 250 mg are clear orange-colored, oblong-shaped, soft gelatin capsules, imprinted "EP138" with white ink and are supplied as follows:

NDC 68382-443-01 in bottles of 100 capsules.

Epilepsy coexist with absence (petit mal). The effectiveness and plasma level determinations.
Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Dispose in a tight container as defined in the USP.

Manufactured by:
Emergo Pharmaceuticals USA Inc.
21-B Center Lane
East Brunswick, NJ 08816

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pomona, NJ 07444

What is ethosuximide?
Ethosuximide is a prescription medicine used to treat absence (petit mal) seizures.

Who should not take ethosuximide capsules?
Do not take ethosuximide capsules if you are allergic to succinimides (methsuximide or ethosuximide), or any of the ingredients in ethosuximide capsules. See the end of this Medication Guide for a complete list of ingredients in ethosuximide capsules.

Who should take ethosuximide capsules?
Do not take ethosuximide capsules if you have a number of people, about 1 in 500.

How to take ethosuximide:
Take ethosuximide exactly as prescribed. Your healthcare provider will tell you how much
ethosuximide to take.

Before you take ethosuximide, tell your healthcare provider if you:

• have or have had liver problems
• have or have had depression, mood problem or suicidal thoughts or behavior
• have any other medical conditions
• are pregnant or plan to become pregnant. It is not known if ethosuximide can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking ethosuximide. You and your healthcare provider should decide if you should take ethosuximide while you are pregnant.
• Take ethosuximide exactly as prescribed. Your health care provider will tell you how much ethosuximide to take.
• Your healthcare provider may change your dose. Do not change your dose of ethosuximide without talking to your healthcare provider.

• If you take too much ethosuximide, call your healthcare provider or your local Poison Control Center right away.

• Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking ethosuximide without first talking to your healthcare provider. Ethosuximide taken with alcohol or

• If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

• Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

• thoughts about suicide or dying
• new or worse depression
• new or worse anxiety
• feeling agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse irritability
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• other unusual changes in behavior or mood

• Call your healthcare provider between visits as needed, especially if you are worried about symptoms:

• irritability
• aggression
• anger
• violence
• acting on dangerous impulses

• Systolic Lupus Erythematosus. Call your healthcare provider right away if you have any of these symptoms:

• joint pain and swelling
• muscle pain
• fatigue
• low-grade fever
• pain in the chest that is worse with breathing
• unexplained skin rash

• Like other antiepileptic drugs, ethosuximide may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

• pain in the chest that is worse with breathing
• red or purple spots on your body
• easy bruising or bleeding gums or nose bleeds
• frequent infections or an infection that does not go away

Rare but serious blood problems that may be life-threatening. Call your healthcare provider right away if you have any of these symptoms:

• pain in the chest that is worse with breathing
• red or purple spots on your body
• easy bruising
• frequent infections or an infection that does not go away

In addition to ethosuximide, you may take other medicines. These other medicines can cause side effects that may affect how ethosuximide works. Do not start or stop any other medicines without talking to your healthcare provider.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription (over-the-counter) medicines, vitamins, and herbal supplements. Taking ethosuximide with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription (over-the-counter) medicines, vitamins, and herbal supplements. Taking ethosuximide with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Take ethosuximide exactly as prescribed. Your health care provider will tell you how much ethosuximide to take.

Your healthcare provider may change your dose. Do not change your dose of ethosuximide without talking to your healthcare provider.

If you take too much ethosuximide, call your healthcare provider or your local Poison Control Center right away.

What should I avoid while taking ethosuximide?
Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking ethosuximide without first talking to your healthcare provider. Ethosuximide taken with alcohol or
medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ethosuximide affects you. Ethosuximide can slow your thinking and motor skills.

What are the possible side effects of ethosuximide?

- Call your healthcare provider right away if you have any of these symptoms:
  - skin rash
  - fever
  - sore in your mouth
  - blisters or peeling skin

Changes in thinking, mood, or behavior. Some patients may get abnormally suspicious thoughts, hallucinations (seeing or hearing things that are not there), or delusions (false thoughts or beliefs).

- Grand mal seizures can happen more often or become worse.

Call your healthcare provider right away, if you have any of the symptoms listed above.

The most common side effects of ethosuximide include:

- nausea or vomiting
- indigestion, stomach pain
- diarrhea
- weight loss
- loss of appetite
- fatigue
- indigestion, stomach pain
- dizziness or lightheadedness
- headache
- loss of concentration
- loss of appetite

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects with ethosuximide. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ethosuximide capsules?

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

Dispense in a tight container as defined in the USP.

- Keep ethosuximide and all medicines out of the reach of children.

General information about ethosuximide

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ethosuximide for a condition for which it was not prescribed. Do not give ethosuximide to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ethosuximide. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ethosuximide that is written for healthcare professionals.

Address medical inquiries to, Telephone: 1-877-993-8779 (MedicalAffairs@zydususa.com).

What are the ingredients in ethosuximide capsules, USP?

Active ingredient: ethosuximide, USP

Capsules inactive ingredients:

FD&C red # 40 aluminum lake, FD&C yellow # 6 aluminum lake, gelatin, glycerin, light mineral oil, methyl paraben, polyethylene glycol, propyl paraben, and sorbitol. The capsule shell is imprinted with white imprinting ink containing opacode white S-1-7078 as colorant which contains the following inactive ingredients: ammonium hydroxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, shellac glaze, stearic acid, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

MF# 0289-01

Manufactured by:
Empaco Pharmaceuticals USA Inc.
25-B Center Lane
East Brunswick, NJ 08816

Distributed by:
Zydus Pharmaceuticals USA Inc
Pennington, NJ 08534

Rev: 05/12
Revision Date: 05/30/2012

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 68382-443-01 in bottle of 100 capsules
Ethosuximide Capsules USP, 250 mg

R

100 Capsules
ZYDUS
Product Characteristics

- **Color**: ORANGE (orange)
- **Shape**: CAPSULE (oblong)
- **Size**: 19mm
- **Flavor**:
- **Imprint Code**: EP138

Packaging

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Marketing Information

- **Labeler**: Zydus Pharmaceuticals (USA) Inc.
- **Registrant**: Zydus Pharmaceuticals (USA) Inc.
- **Establishment Name**: Emcure Pharmaceuticals USA Inc.
- **Business Operations**: Analysis(68382-443), Manufacture(68382-443)

Revised: 5/2012