

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ETHOSUXIMIDE EQUITY 250 mg/5 mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of oral solution contains 250 mg ethosuximide (50 mg/mL).

Excipient(s) with known effect:

Sodium benzoate 2,5 mg/5 mL (0,5 % w/v) as preservative.

Propylene glycol 3,7 mg/5 mL (0,74 mg/mL).

Sucralose 5 mg/5 mL (1 mg/mL) as sweetener.

Contains sugar (glycerol 400 mg/5 mL (80 mg/mL)).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, colourless solution with characteristic strawberry odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Initial dose	3 to 6 years:	5 mL (250 mg)/day
	6 years and older:	10 mL (500 mg)/day

Usage in children below 3 years of age:

Safety and effectiveness in patients below the age of 3 years have not been established.

Maintenance therapy:

The dosage must be individualised according to the patient's clinical response. Dosage should be increased by small increments. One useful method is to increase the daily dosage by 250 mg every four to seven days until control is achieved with minimal side effects. Dosages exceeding 1,5 g daily for an adult, in divided doses should be administered only under the strictest supervision by a healthcare professional with appropriate expertise. The optimal dose for most children is 20 mg/kg/day. This dose has given average plasma levels within the accepted therapeutic range of 40 to 100 µg/mL.

Method of administration

For oral use.

A 10 mL graduated oral syringe and a bottle neck adaptor are provided to aid dosing.

4.3 Contraindications

- Hypersensitivity to succinimides, ethosuximide, or to any of the excipients listed in section 6.1.
- Porphyrias.
- Ethosuximide as contained in ETHOSUXIMIDE EQUITY, is contraindicated in mixed types of epilepsy, may increase the frequency of generalised tonic clonic (grand mal) seizures in some patients.

4.4 Special warnings and precautions for use***General***

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs (AEDs), including ETHOSUXIMIDE EQUITY, 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 EQUITY. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered and the patient be referred for psychiatric evaluation. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Patients treated with ETHOSUXIMIDE EQUITY should be routinely evaluated for depression and anxiety.

It is important to proceed slowly when increasing or decreasing the dosage, as well as when adding or removing other medication. Abrupt withdrawal of ETHOSUXIMIDE EQUITY 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 $3\,500/\text{mm}^3$ or a granulocyte ratio of less than 25 %, the dose should be reduced, or the ETHOSUXIMIDE EQUITY discontinued.

Hepatic/renal impairment

Ethosuximide as contained in ETHOSUXIMIDE EQUITY should be used with extreme caution in patients with impaired hepatic or renal function. The liver enzymes should also be checked regularly (initially monthly, after one year every six months).

Periodic urinalysis and liver function studies are advised for all patients receiving the medicine.

Ethosuximide as contained in ETHOSUXIMIDE EQUITY 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 as contained in ETHOSUXIMIDE EQUITY. Additionally, lupus-like reactions have been reported in children given ETHOSUXIMIDE EQUITY. 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 ETHOSUXIMIDE EQUITY 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 medicines, 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 medicine 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 and ETHOSUXIMIDE EQUITY withdrawn.

ETHOSUXIMIDE EQUITY 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 medicine), patients who have a

family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitised 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 ethosuximide as contained in ETHOSUXIMIDE EQUITY.

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 healthcare practitioner 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, ETHOSUXIMIDE EQUITY treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of ETHOSUXIMIDE EQUITY. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of ethosuximide, ETHOSUXIMIDE EQUITY must not be re-started in this patient at any time. Patients should be advised to wear a medic-alert bracelet or pendant to let healthcare providers know of previous serious reactions related to ethosuximide as contained in ETHOSUXIMIDE EQUITY.

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 medicines associated with SJS/TEN, including ethosuximide. If these patients are known to be positive for HLA-B*1502, ETHOSUXIMIDE EQUITY should not be used.

Information for patients

Patients taking ETHOSUXIMIDE EQUITY should be advised of the importance of adhering strictly to the prescribed dosage regimen.

Patients should be instructed to promptly contact their healthcare practitioner if they develop signs and/or symptoms (e.g., sore throat, fever) suggesting an infection.

Withdrawal

ETHOSUXIMIDE EQUITY should always be withdrawn slowly. If ETHOSUXIMIDE EQUITY is being substituted for another anti-epileptic medicine it must not be withdrawn abruptly but the replacement made gradually with overlap of the new preparation otherwise break through petit mal seizures may occur.

ETHOSUXIMIDE EQUITY contains sodium benzoate, sodium and propylene glycol

ETHOSUXIMIDE EQUITY contains 2,5 mg sodium benzoate in each 5 mL dose which is equivalent to 0,5 mg/mL. An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

ETHOSUXIMIDE EQUITY contains less than 1 mmol sodium (23 mg) per 5 mL, that is to say essentially 'sodium-free'.

ETHOSUXIMIDE EQUITY contains 3,7 mg propylene glycol in each 5 mL. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicines and other forms of interaction

ETHOSUXIMIDE EQUITY may interact with concurrently administered antiepileptic medicines, periodic serum level determinations of these medicines may be necessary (e.g., ethosuximide may elevate

phenytoin serum levels and valproic acid has been reported to both increase and decrease ethosuximide levels).

The plasma concentrations of ethosuximide may be reduced by carbamazepine, primidone, phenobarbitone and lamotrigine and increased by isoniazid.

4.6 Fertility, pregnancy and lactation

Safe usage of ETHOSUXIMIDE EQUITY in pregnancy and breastfeeding mothers is unknown.

Pregnancy

Cases of birth defects have been reported with ethosuximide as contained in ETHOSUXIMIDE EQUITY. Ethosuximide crosses the placenta. Reports suggest an association between the use of other anticonvulsant medicines by women with epilepsy and an elevated incidence of birth defects in children born to those women.

Breastfeeding

Ethosuximide is excreted into breast milk.

Because the effects of ETHOSUXIMIDE EQUITY on nursing infants are unknown, caution should be exercised when ETHOSUXIMIDE EQUITY is administered to a breastfeeding mother.

4.7 Effects on ability to drive and use machines

ETHOSUXIMIDE EQUITY 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

Tabulated list of adverse reactions

* Adverse effects frequency estimated from post-marketing safety database.

MedDRA System Organ Class	Frequency†	Undesirable Effects
Blood and lymphatic system disorders	Less frequent	Agranulocytosis*, aplastic anaemia*, eosinophilia*, leukopenia*, pancytopenia*, bone marrow failure
	Frequency unknown	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity*
Metabolism and nutrition disorders	Frequent	Decreased appetite
Psychiatric disorders	Frequent	Irritability
	Less frequent	Aggression*, sleep terror*, depression*, suicidal ideation*, psychotic disorder*, sleep disorder*
	Frequency unknown	Euphoric mood, apathy, increased libido
Nervous system disorders	Frequent	Headache, ataxia, dizziness, drowsiness, somnolence
	Less frequent	Psychomotor hyperactivity*, lethargy, disturbance in attention*
	Frequency unknown	Extrapyramidal side effects, increased frequency of grand mal convulsions
Eye disorders	Less frequent	Myopia*
Respiratory, thoracic and mediastinal disorders	Frequent	Hiccups
Gastrointestinal disorders	Frequent	Abdominal pain, cramps, upper

		abdominal pain, nausea, gastrointestinal disorder, abdominal discomfort, vomiting
	Less frequent	Diarrhoea, gingival hypertrophy*, swollen tongue*
Skin and subcutaneous tissue disorders	Frequent	Rash erythematous, urticaria
	Less frequent	Stevens-Johnson syndrome*
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Less frequent	Systemic lupus erythematosus*
Renal and urinary disorders	Less frequent	Haematuria*, proteinuria
Reproductive system and breast disorders	Less frequent	Vaginal haemorrhage*
General disorders and administration site conditions	Less frequent	Fatigue
Investigations	Less frequent	Decreased weight

Description of selected adverse reactions

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 medicine is important. It allows continued

monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>.

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 2 g have been taken, fluids should be given by mouth. If a larger dose has been taken breathing should be assessed and managed properly, and any other symptoms treated accordingly. Activated charcoal is known to be used in the treatment of overdosage in conscious patients who are able to protect their airway. Haemodialysis may be useful. Forced diuresis and exchange transfusions are ineffective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants including anti-epileptics.

Pharmacotherapeutic group: Succinimide derivatives, ATC code: N03AD01

Mechanism of action

Ethosuximide an oral succinimide anticonvulsant, chemically designated as alpha-ethyl-alpha-methyl-succinimide.

Ethosuximide suppresses the paroxysmal three-cycle-per-second spike and wave activity associated with lapses of consciousness which are 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.

5.2 Pharmacokinetic properties

Absorption

Ethosuximide is readily absorbed from the gastrointestinal tract and extensively metabolised in the liver.

Distribution

Ethosuximide is widely distributed throughout the body but is not significantly bound to plasma proteins.

Biotransformation

Peak serum levels occur 1 to 7 hours after single oral dose. Therapeutic levels are between 40 and 100 µg/mL. It has a long elimination half-life: adults 40 to 60 hours; children 30 hours.

Elimination

It is excreted in the urine mainly in the form of its metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous (E330)

Glycerol (E422)

Sodium benzoate (E211)

Sodium citrate (E331 iii)

Strawberry flavour (including propylene glycol, E1520)

Sucralose (E955)

Hydrochloric acid, concentrated (E507) (for pH adjustment)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store at or below 25 °C. Do not refrigerate or freeze.

After first opening use within two months.

6.5 Nature and contents of container

ETHOSUXIMIDE EQUITY is filled into amber, Type III glass bottles of 200 mL nominal capacity, suitable for pharmaceutical use, safely sealed with a HDPE child-resistant and tampered evident screw cap with LDPE seal, placed in an outer carton. Each bottle contains 200 mL solution.

A 10 mL oral syringe of 0,5 mL graduations along with a bottle neck adaptor, are also provided.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

57/2.5/0200

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 April 2025

10. DATE OF REVISION OF THE TEXT