Professional Information

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ETHOSUXIMIDE MC PHARMA

Strength

250 mg/5 ml

Pharmaceutical form

Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of ETHOSUXIMIDE MC PHARMA contains 250 mg Ethosuximide (50 mg/mL).

Excipient(s) with known effect:

Contains sugar and sweetener.

Sucrose 3 g/5 ml

Saccharin sodium 8.325 mg/5 ml

This medicine contains 11,9 mg Sodium benzoate in each 5 ml which is equivalent to 2,38 mg/ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A clear slightly yellowish liquid with a characteristic odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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4.2 Posology and method of administration

Posology

Paediatric population

Initial dose:

Ages 3 to 6 years: 250 mg (5 ml) per day.

Ages 6 years and older: 500 mg (10 ml) per day.

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

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 of the medical practitioner. 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 - 100 µg/mL.

Method of administration

For oral use

4.3 Contraindications

- ETHOSUXIMIDE MC PHARMA is contraindicated in patients with hypersensitivity to succinimides, ethosuximide or any of the ingredients of this medicine. (See section 6).
- **Porphyrias**

  Ethosuximide as contained in ETHOSUXIMIDE MC PHARMA, is contraindicated in mixed types of epilepsy, may increase the frequency of generalised tonic clonic (grand mal) seizures in some patients.

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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 MC PHARMA, 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 MC PHARMA. 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 MC PHARMA 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 MC PHARMA may precipitate absence (petit mal) seizures.

- Patients taking ETHOSUXIMIDE MC PHARMA should be advised of the importance of adhering strictly to the prescribed dosing regimen.
- **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/mm³ or a granulocyte ratio of less than 25 %, the dose should be reduced, or the ETHOSUXIMIDE MC PHARMA discontinued.
- **Blood dyscrasias**, including some with fatal outcome, have been reported to be associated with the use of medicines containing ethosuximide; therefore, periodic blood count determinations should be performed. Should signs and/or symptoms of infection (e.g. sore throat fever) develop, blood count determinations should be considered at that point. (See section 4.8).

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- Avoid use of ETHOSUXIMIDE MC PHARMA in patients with history of ethosuximide-induced DITP. Drug-induced immune thrombocytopenia (DITP) has been reported with use of ethosuximide. When DITP is suspected, discontinue use of ETHOSUXMIDE MC PHARMA, monitor serial platelet counts, and treat as appropriate. Assess the presence of drug-dependent antiplatelet antibodies, if possible. (See section 4.8).
- ETHOSUXIMIDE MC PHARMA should be administered with extreme caution to patients with known liver or renal diseases. Periodic urinalysis and liver function studies are advised for all patients under treatment. ETHOSUXIMIDE MC PHARMA is capable of producing morphological and functional changes in the animal liver. In humans, abnormal liver and renal function studies have been reported. (See section 4.8).
- Cases of systemic lupus erythematosus have been reported with the use of medicines containing ethosuximide. The medical practitioner should be alert to this possibility. Cases of a systemic hypersensitivity syndrome with fever, lymphadenopathy, eosinophilia, lymphocytosis and rash have been reported. (See section 4.8).
- 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 MC PHARMA. 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 MC PHARMA treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of ETHOSUXIMIDE MC PHARMA. Early withdrawal is associated with a better prognosis. If the patient has

developed SJS or TEN with the use of ethosuximide, ETHOSUXIMIDE MC PHARMA 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 MC PHARMA.

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 MC PHARMA should not be used.

- Severe Cutaneous Adverse Reactions (SCARs)

  Hypersensitivity Syndrome (HSS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi organ hypersensitivity, has been reported with medicines containing ethosuximide. Patients should be monitored for early signs of hypersensitivity such as fever, rash or lymphadenopathy. (See section 4.8).

- 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 MC PHARMA

withdrawn. 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.

- Withdrawal

  ETHOSUXIMIDE MC PHARMA should always be withdrawn slowly. If ETHOSUXIMIDE MC PHARMA 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 MC Pharma may be used as chronic treatment for the control of absence (petit mal) epilepsy.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). 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). (See section 2).

Paediatric population

Do not give ETHOSUXIMIDE MC PHARMA to children below the age of 3 as safety and effectiveness has not been established. (See section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Since ETHOSUXIMIDE MC PHARMA may interact with concurrently administered anti-epileptic medicines, periodic serum level determinations of these medicines may be necessary (e.g. ethosuximide may elevate phenytoin serum levels whereas valproic acid has been reported to increase or decrease ethosuximide levels due to changes in metabolism).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Caution should be exercised when prescribing Ethosuximide MC Pharma to Women of childbearing potential. The patient should be advised of the potential risks.

Pregnancy

Safe usage of ETHOSUXIMIDE MC PHARMA in human pregnancy is not documented. Ethosuximide crosses the placenta. Cases of birth defects have been reported with use of ethosuximide in pregnancy.

Breastfeeding

Ethosuximide is excreted in human breast milk. As the effects of ETHOSUXIMIDE MC PHARMA on nursing infants are unknown, caution should be exercised when ETHOSUXIMIDE MC PHARMA is administered to a nursing mother.

Fertility

No fertility data available

4.7 Effects on ability to drive and use machines

ETHOSUXIMIDE MC PHARMA 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. (See section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Frequent undesirable effects include anorexia, abdominal pain, cramps, epigastric pain, vague gastric upset, nausea, vomiting.

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b. Tabulated list of adverse reactions

The table below contains side-effects categorized as follows utilizing the incidence rates: frequent ≥ 1/10 (≥ 10 %); frequent ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); less frequent ≥ 1/1000 and < 1/100 (≥ 0,1 % and < 1 %), less frequent ≥ 1/10 000 and < 1/1000 (≥ 0,01 % and < 0,1 %); less frequent < 1/10 000 (< 0,01 %).

System Organ Class	Frequency	Undesirable Effects
Blood and Lymphatic System Disorders	*Less frequent*	Leukopenia
	Less frequent	Agranulocytosis, aplastic anaemia eosinophilia, pancytopenia with or without bone marrow suppression. thrombocytopenia
Immune System Disorders	*Less frequent*	Allergic reaction
Metabolism and Nutrition Disorders	*Frequent*	Decreased appetite, Anorexia
Psychiatric Disorders	*Frequent*	Aggressiveness, euphoria, irritability
	Less frequent	Depression with overt suicidal intentions, disturbances of sleep, increased libido, increased state of paranoid psychosis, night terrors
Nervous System Disorders	*Frequent*	Dizziness, drowsiness, headache, hyperactivity
	Less frequent	Ataxia, inability to concentrate
Eye Disorders	*Less frequent*	Myopia
Respiratory, Thoracic and Mediastinal Disorders	*Frequent*	Hiccups
Gastrointestinal Disorders	*Frequent*	Abdominal pain, cramps, epigastric pain,

System Organ Class	Frequency	Undesirable Effects
		vague gastric upset, nausea, vomiting
	Less frequent	Diarrhoea, gum hypertrophy, tongue swelling
Skin and Subcutaneous Tissue Disorders	*Frequent*	Pruritic erythematous rashes, urticaria
	Less frequent	Stevens-Johnson syndrome, rash, petechiae
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 bleeding
General Disorders and Administration Site Conditions	*Less frequent*	Fatigue, lethargy
Investigations	*Less frequent*	Weight loss

c. 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 requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Acute overdose may produce nausea, vomiting and CNS depression including coma with respiratory depression. A relationship between ethosuximided toxicity and its plasma levels has not been established.

Treatment:

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 Anti-convulsants including anti-epileptics

Pharmacotherapeutic group: Succinimide derivatives, ATC code: N03AD01.

Ethosuximide is an oral succinimide anti-convulsant, 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 completely and rapidly absorbed from the gastrointestinal tract and extensively metabolised in the liver.

Distribution

Ethosuximide is not significantly bound to plasma proteins therefore, the drug is present in saliva and cerebrospinal fluid in concentrations approximately equal to that of the plasma.

Biotransformation

Peak serum levels occur 1 to 7 hours after single oral dose. Therapeutic concentrations are in the range of 40 - 100 µg/ml. Ethosuximide is extensively metabolised to at least three plasma metabolites. It has a long elimination half-life: adults 40 to 60 hours; children 30 hours.

Elimination

Only 12 – 20 % of the drug is excreted unchanged in the urine.

Paediatric population

Steady-state conditions are achieved after approximately 6 days in children. The peak levels in children occur within 3 to 7 hours. elimination half-life for the drug 40-60 hours in adults and 30 hours in children.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- saccharin sodium
- sucrose
- glycerol
- sodium citrate
- sodium benzoate
- purified water
- raspberry flavour

6.2 Incompatibilities

Not applicable

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6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

Protect from freezing and light.

6.5 Nature and contents of container

A 200 ml round amber glass bottle and white polypropylene screw on cap and outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

MC Pharma (Pty) Ltd

62 Constantia Avenue

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Centurion

0157

8 REGISTRATION NUMBER

57/2.5/0848

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2025

10 DATE OF THE REVISION OF TEXT