SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethosuximide G.L. Pharma 250 mg/5 ml oral solution sugar free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 50 mg ethosuximide.

Excipient with known effect:
1 ml oral solution contains 1 mg methyl parahydroxybenzoate (E 128).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution
Clear, slightly viscous, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Pyknoleptic absences as well as complex and atypical absences
- Myoclonic-astatic petit mal and myoclonic fits of adolescents (impulsive petit mal), if other medicinal products are not effective and/or are not tolerated

4.2 Posology and method of administration

Posology

Adults, elderly patients and children over 6 years of age: The treatment is started at a daily dose of 500 mg.

Depending on the patient's tolerance, the dose is increased every five to seven days in increments of max. 250 mg until the seizures are controlled by a daily dose of 1000-1500 mg. In an individual case, a daily dose of 2000 mg, taken in several single doses, may be required.

The therapeutic plasma level of ethosuximide is normally between 40 and 100 µg/ml. However, the dose depends on the patient's clinical response. The half-life of ethosuximide in plasma is more than 24 hours so that the daily dose can be taken as a single dose provided the medicinal product is well tolerated. Higher daily doses should be taken in 2 or 3 single doses, however.

The probability of dose-dependent undesirable effects can be reduced by careful dosing (small initial dose at the start of treatment, gradual increase of dose) and by taking the medicinal product during or after meals.

Antiepileptic therapies are principally long-term therapies. A specialist (neurologist, neuropaediatrician) should decide about the start, duration and discontinuation of ethosuximide on an individual basis.

In general, reduction of the dose and discontinuation of the medicinal product should not be considered before the patient has been free from fits for 2-3 years.

The medicinal product must be discontinued by reducing the dose gradually over a period of one to two years. Children may be allowed to outgrow the dose per kg body weight instead of adjusting the dose according to their age, however, it must be ensured that the EEC findings do not deteriorate.

Special populations

Haemodialysis patients

Ethosuximide is dialysable. Haemodialysis patients therefore require a supplementary dose or a modified dose regimen. During a dialysis period of four hours, 39% to 52% of the dose taken is removed.

Paediatric population

Children under 2 years

The treatment is started at a daily dose of 125 mg (2.5 ml). The dose is increased gradually in small increments every few days until the fits are controlled.

Children between 2 and 6 years

The treatment is started at a daily dose of 250 mg (5 ml). The dose is increased gradually in small increments every few days until the fits are controlled.

The optimum daily dose for most children is 20 mg/kg. The maximum daily dose is 1000 mg.

The data available from clinical studies of the use of ethosuximide in children and adolescents are described in section 5.1.

Method of administration

Oral use.

The solution can be taken during or after meals.

The pack contains a 10 ml graduated oral syringe (0.5 ml steps) and an adapter for the oral syringe. A single dose of the oral solution is drawn into the oral syringe up to the required level and transferred into a glass of water or mixed with milk porridge or pudding.

Alternatively, the oral solution can directly be applicated into the mouth. Afterwards, the patient should drink half a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance, other succinimides, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

If dyskinesias occur (see section 4.8), ethosuximide must be discontinued and diphenhydramine administered by the intravenous route, if required.

Special attention should be given to clinical symptoms of bone marrow damage (fever, angina, haemorrhage). 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 3500/mm^3 or a granulocyte ratio of less than 25%, the dose should be reduced or the therapy discontinued. The liver enzymes should also be checked regularly.

In particular in patients with a history of psychiatric disorders psychic undesirable effects (see section 4.8, paranoid and hallucinatory symptoms, anxiety, agitation) may occur, therefore special caution is required when treating this group of patients with ethosuximide.

Suicidal ideation and behaviour

Suicidal thoughts and behaviour have been reported in patients treated with antiepileptics for various indications. A meta-analysis of randomised, placebo-controlled studies with antiepileptics also showed a slightly increased risk for suicidal thoughts and behaviour. The mechanism triggering this undesirable

effect is unknown, and the data available do not exclude a potentially increased risk when taking ethosuximide.

Therefore, patients should be monitored for the emergence of suicidal thoughts and behaviour, and an appropriate treatment should be considered. Patients (and their caregivers) should be advised to seek medical help if symptoms of suicidal thoughts or behaviour occur.

Note:

To prevent grand fits which are often associated with complex and atypical absences, ethosuximide can be combined with effective anticonvulsives (e.g. primidone or phenobarbital). Additional grand mal prophylaxis can be dispensed with only in the case of pyknoleptic absence epilepsies in children of school age.

Severe skin reactions

Serious dermatologic reactions, including Stevens-Johnson Syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with ethosuximide treatment. SJS and DRESS can be fatal. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ethosuximide should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Excipients with known effects

This medicinal product contains methyl parahydroxybenzoate (E 218), which may cause allergic reactions, possibly delayed.

This medicinal product contains less than 1 mmol (23 mg) sodium per ml, i.e. it is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In particular the following interaction of ethosuximide with other medicinal products should be considered:

Effects of other medicinal products on ethosuximide

The concomitant administration of carbamazepine increases the plasma clearance of ethosuximide. Valproic acid may increase the plasma concentration of ethosuximide in most patients.

Effects of ethosuximide on other medicinal products

Ethosuximide normally does not change the plasma concentration of other antiepileptics such as primidone, phenobarbital, and phenytoin since

ethosuximide is not an enzyme inductor. However, individual cases of elevated phenytoin concentration were reported when ethosuximide was administered concomitantly.

The simultaneous use of medicinal products affecting the central nervous system, alcohol or convulsion-inducing substances and ethosuximide should be avoided.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised by their doctor of the necessity of planning and monitoring a pregnancy before starting the treatment with ethosuximide. Patients should be advised to tell their doctor immediately if they have become pregnant during the treatment.

Pregnancy

The treatment with ethosuximide should not be interrupted during pregnancy without the consent of a physician as the sudden discontinuation of the treatment or uncontrolled reduction of the dose may result in recurrence of epileptic seizures, which may harm the pregnant woman and/or the unborn child.

Ethosuximide crosses the placenta. Studies in animals have shown reproductive toxicity (see section 5.3). Specific congenital malformations have not been observed in children of mothers exposed to ethosuximide monotherapy during pregnancy. The risk of malformations during anti-epileptic therapy is increased by a factor of 2 to 3 compared to the expected incidence of about 3% in the general population. Most common malformations reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapies are associated with a higher risk of congenital malformation, so that monotherapy should be practised during pregnancy whenever possible.

Patients should be informed of the increased risk of malformations and prenatal diagnostic measures should be offered.

The lowest effective dose ensuring seizure control must not be exceeded, particularly during the 20^{th} and 40^{th} day of pregnancy. The ethosuximide serum concentration of the pregnant woman must be regularly monitored.

Folic acid supplementation is recommended in patients planning to have a baby and during pregnancy. To prevent vitamin K_1 deficiency and reduce the risk for haemorrhages in newborn infants, women should be given vitamin K_1 during the last month of pregnancy.

Breast-feeding

Ethosuximide is excreted into breast milk reaching concentrations up to 94% of the maternal serum concentrations (see section 5.2). Sedation, poor suckling and irritability have been observed in individual breast-fed infants.

Breast-feeding should be discontinued during treatment with ethosuximide.

4.7 Effects on ability to drive and use machines

During the adjustment phase, at higher doses and in combination with other medicinal products affecting the central nervous system reactivity can be impaired to an extent that the ability to drive or operate machines is affected. This may even be the case when ethosuximide is taken as prescribed, and especially in connection with alcohol.

Therefore patients should not drive, operate machines or perform any other potentially hazardous activities, at least not during the adjustment phase of the treatment. The decision will be taken in each case by the attending doctor considering the patient's individual response and the respective dose.

4.8 Undesirable effects

Summary of safety profile

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).

Within the therapeutic dose range undesirable effects are common and have been observed in about 1/6 of patients. These are mainly nausea, vomiting, singultus and abdominal pain.

Tabulated list of adverse reactions

The frequency of possible undesirable effects is defined using the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1 000 to < 1/100)
Rare (≥ 1/10 000 to < 1/1 000)
Very rare (< 1/10 000)
Not known (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders

Rare:	Leucopenia*, thrombocytopenia*, agranulocytosis*, eosinophilia*
Not known:	In individual cases aplastic anaemia* and pancytopenia* have been observed.

Metabolism and nutrition disorders
Uncommon: Loss of weight, loss of appetite

Psychiatric disorders
Uncommon: Withdrawal, anxiety, sleep disturbances
Rare: Paranoid and hallucinatory phenomena developing over days and weeks

Nervous system disorders
Uncommon: Severe headache, ataxia, lethargy
Not known: A few individual cases of dyskinesia have been reported for the period of the first 12 hours after start of the treatment; it disappeared soon after discontinuation of ethosuximide or the administration of diphenhydramine.

Respiratory, thoracic and mediastinal disorders
Common to very common: Singultus

Gastrointestinal disorders
Common to very common: Nausea, vomiting, abdominal pain
Uncommon: Diarrhoea, constipation

Skin and subcutaneous tissue disorders
Rare: Lupus erythematodes of varying extent*
Not known: Allergic skin reactions*, such as exanthema, but also the severe generalised form of Stevens-Johnson syndrome*, or drug reaction with eosinophilia and systemic symptoms (DRESS) may occur.

* Effect independent of the dose (also see section 4.2)

If undesirable effects occur which are independent of the dose taken and reversible, the medicinal product should be discontinued. They may reappear when the medicinal product is taken again.

Long-term treatment may affect the patient's performance, e.g. the performance in school of children and adolescents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Whenever evaluating an overdose, potential multiple intoxication should principally not be excluded e.g. several medicinal products have been taken with a suicidal intent. The symptoms of overdose are potentiated under the influence of alcohol and other CNS depressants.

Symptoms of intoxication
Ethosuximide has a low toxicity. The symptoms listed as undesirable effects such as tiredness, lethargy, depression and agitation, also irritability, are more frequent or severe in the case of intoxication.

If intoxication is suspected, it is recommended to determine the plasma concentration of the antiepileptics.

Treatment of intoxication
Significant overdoses require initial gastric lavage and the administration of activated charcoal as well as monitoring of the cardiovascular and respiratory systems in an intensive care unit. There is no specific antidote. Haemodialysis may be useful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, succinimide derivatives
ATC code: N03AD01

Ethosuximide is an antiepileptic of the class of succinimides that apparently exerts multiple mechanisms of action. The activity of ethosuximide in absence type epilepsy seems to rely primarily on the inhibition of T-type calcium channels in the thalamus.

Paediatric population
In a double-blind, randomised study of 20 weeks duration in 453 children aged 2.5 to 13 years with newly diagnosed childhood absence epilepsy, the efficacy, tolerance, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine as monotherapy in childhood absence epilepsy were studied. Those treated with either ethosuximide or valproic acid had higher freedom-from-failure rates (53% and 58%, respectively) than those given lamotrigine (29%, odds ratio with ethosuximide vs. lamotrigine, 2.66; 95% confidence interval [CI], 1.65 to 4.28; odds ratio with valproic acid vs. lamotrigine, 3.34; 95% CI, 2.06 to 5.42; $p<0.001$ for both comparisons). In both pre-specified and post hoc analyses, ethosuximide resulted in fewer attentional effects as

compared with valproic acid (at week 16 and week 20, the percentage of test subjects with a confidence index score of 0.60 or higher in the Conners' Continuous Performance Test was greater in the valproic acid group than in the ethosuximide group (49% vs. 33%; odds ratio, 1.95; 95% CI, 1.12 to 3.41; p=0.03) and the lamotrigine group (49% vs. 24%; odds ratio, 3.04; 95% CI, 1.69 to 5.49; p<0.001).

5.2 Pharmacokinetic properties

Absorption

Ethosuximide is practically completely absorbed after oral administration. C_{max} values of 18-24 µg/ml were measured after the intake of 1 g ethosuximide in three test persons after 1-4 hours.
In adults under long-term treatment at a dose of ca. 15 mg/kg body weight a plasma concentration of about 50 µg/ml was measured. At an oral dose of 1 mg/kg per day, a plasma concentration of 2-3 µg/ml is to be expected. Steady state is expected to occur 8-10 days after start of treatment. Despite significant interindividual variation of plasma concentrations at the same oral dose, a dose-linear dependence of plasma concentration was established.
The therapeutic plasma concentration of ethosuximide is 40-100 µg/ml. Plasma concentrations of more than 150 µg/ml may lead to toxic effects.

Distribution

Ethosuximide is not bound to plasma proteins.
Ethosuximide is present in liquor and saliva in the same concentration as in plasma. The apparent volume of distribution is specified to be 0.7 l/kg body weight.

Biotransformation

Ethosuximide is extensively metabolised in the liver by oxidation. Several metabolites are produced, in particular the two diastereomers of 2-(1-hydroxyethyl)-2-methylsuccinimide and of 2-ethyl-2-methyl-3-hydroxy-succinimide. The metabolites are probably inactive.

Elimination

Between 10% and 20% of ethosuximide only is excreted unchanged in the urine. The main metabolites of ethosuximide, the two diastereomers of 2-(1-hydroxyethyl)-2-methyl succinimide and 2-ethyl-2-methyl-3-hydroxy-succinimide, are to some extent conjugated and excreted renally as glucuronide.
After a single oral dose of 13.1-18.0 mg ethosuximide/kg body weight given to 12 male test persons (20-23 years, 57.2-114.8 kg body weight), a plasma half-livese of 38.3-66.6 hours were measured.

After a single dose of 500 mg ethosuximide (capsules) given to 5 children, plasma half-lives of 25.7-35.9 hours were measured, with oral solution the plasma half-lives were 24.8-41.7 hours.

Passage into breast milk

Ethosuximide passes into breast milk: the ratio of the ethosuximide concentration of breast milk vs. plasma is specified to be 0.94 ± 0.06.

Paediatric population

In a study in children (7-8.5 years, 12.9-24.4 kg body weight) C_{max} values of 28.0-50.9 µg/ml were measured 3-7 hours after the children had taken a single dose of 500 mg ethosuximide.
Long-term treatment of children at 20 mg/kg body weight produces a plasma concentration of approximately 50 µg/ml. In children an oral daily dose of 1 mg/kg produces a plasma concentration of 1-2 µg/ml. Therefore, younger children require a slightly higher dose than older children.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity.

Ethosuximide did not reveal a potential for mutagenicity or chromosome aberrations when studied *in vitro*.

Long-term studies of the carcinogenetic potential in animals have not been performed.
Embryotoxicity studies in rats and mice revealed a higher incidence rate of malformation and changes in behaviour.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E 218)
Macrogol 300
Hypromellose
Sucralose
Sodium citrate dihydrate
Citric acid monohydrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Shelf life after first opening: 6 months.

6.4 Special precautions for storage

This medical product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle (glass type III) with child-resistant closure (polypropylene/polyethylene) and an adapter for the oral syringe.
Packs of 125 ml, 200 ml, or 250 ml oral solution in a carton with a 10 ml graduated oral syringe, graduated in 0.5 ml steps.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH
Schlossplatz 1
8502 Lannach
Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/02/2024

10 DATE OF REVISION OF THE TEXT

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