SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethosuximide Strides 250mg/5ml Syrup

Epesri 250mg/5ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 250 mg ethosuximide.

Excipients with known effect:

Each 5 ml contains 1.5 mg sucrose, 200 mg glucose and 10 mg sodium benzoate (E211).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

A clear colourless to slightly yellowish solution with an aroma of raspberry flavour.

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 petitmal), 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.

Anti-epileptic 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.

Children-

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

Ethosuximide Strides is for oral use.

The pack contains a measuring cup graduated from 2.5 ml to 15 ml to adjust the doses.

The solution can be taken during or after meals.

4.3 Contraindications

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

Porphyrias.

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/mm3 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 anti-epileptics 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.

All patients treated with AEDs should be routinely evaluated for depression and anxiety.

Ethosuximide, when used alone in mixed types of epilepsy, may increase the frequency of generalised tonic clonic (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) seizures.

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.

Hepatic/Renal Impairment
Ethosuximide should be used with extreme caution in patients with impaired hepatic or renal function.

Periodic urinalysis and liver function studies are advised for all patients receiving the drug. Ethosuximide 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. The physician should be alert to this possibility. Additionally, lupus-like reactions have been reported in children given ethosuximide. 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 drug 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 drugs, 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 drug 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.

Ethosuximide 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 drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized 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. 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 physician 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 treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of ethosuximide, ethosuximide must not be re-started in this patient at any time.

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 drugs associated with

SJS/TEN, including ethosuximide. If these patients are known to be positive for HLA-B*1502, the use of ethosuximide should only be considered if the benefits are thought to exceed the risks.

In the Caucasian and Japanese population, the frequency of HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

Information for Patients
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 if they develop signs and/or symptoms (e.g. sore throat, fever) suggesting an infection.

Withdrawal
If ethosuximide is being substituted for another anti-epileptic drug the latter must not be withdrawn abruptly but the replacement made gradually with overlap of the preparations otherwise petit mal may break through.

Ethosuximide should always be withdrawn slowly.

Excipients

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase should not take this medicine. May be harmful to teeth.

Glucose
Patients with rare glucose-galactose malabsorption should not take this medicine. May be harmful to teeth.

Sodium benzoate (E211)
This medicine contains 10 mg sodium benzoate (E211) in each 5 ml syrup which is equivalent to 2 mg/ml. Sodium benzoate (E211) 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).

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 5 ml syrup, this is to say 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 phenytoine 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.

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).

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

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. Reports suggest an association between the use of other anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to those women. Cases of birth defects have been reported with ethosuximide. 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 20th and 40th 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 K1 deficiency and reduce the risk for haemorrhages in newborn infants, women should be given vitamin K1 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.

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.

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).

Psychiatric or psychological aberrations associated with ethosuximide administration may be noted particularly in patients who have previously exhibited psychological abnormalities.

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)
*AE frequency estimated from post-marketing safety database

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	Uncommon	Agranulocytosis*, Aplastic anaemia*, Eosinophilia*, Leukopenia*, Pancytopenia*, Bone marrow failure
	Not Known	Thrombocytopenia
Immune system disorders	Uncommon	Hypersensitivity*
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Uncommon	Aggression*, Sleep terror*, Depression*, Suicidal ideation*, Psychotic disorder*, Sleep disorder*
	Not known	Euphoric mood, Apathy, Libido increased
Nervous system disorders	Common	Headache, Ataxia, Dizziness, Somnolence
	Uncommon	Psychomotor hyperactivity*, Lethargy, Disturbance in attention*
	Not Known	Extrapyramidal side effects, Increased frequency of grand mal convulsions
Eye disorders	Uncommon	Myopia*
Respiratory, thoracic and mediastinal disorders	Uncommon	Hiccups
Gastrointestinal disorders	Common	Abdominal pain, Abdominal pain upper, Gastrointestinal disorder, Nausea, Abdominal discomfort, Vomiting
	Uncommon	Diarrhoea, Gingival hypertrophy*, Swollen tongue*
Skin and subcutaneous tissue disorders	Common	Rash erythematous, Urticaria
	Uncommon	Stevens-Johnson syndrome*
	Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	Systemic lupus erythematous*
Renal and urinary	Uncommon	Haematuria*

disorders		
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage*
General disorders and administration site conditions	Uncommon	Fatigue, Irritability*
Investigations	Uncommon	Weight decreased

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: Anti-epileptics, succinimide derivatives,

ATC code: N03AD01

Ethosuximide is an anti-epileptic 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.

Children and adolescents

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 weeks 16 and 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, 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 have 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 approximately 0.7 l/kg body weight.

Biotransformation

Ethosuximide is extensivly metabolised in the liver by oxidation. Several metabolites are produced, in particular the two diastereomeres of 2-(1-hydroxyethyl)-2-methyl succinimide and of 2-ethyl-2-methyl-3-hydroxysuccinimide. 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 diastereomeres of 2-(1-hydroxyethyl)-2-methyl succinimide and of 2-ethyl-2-methyl-3-hydroxysuccinimide 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) plasma half-lives 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) Cmax 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

Sodium benzoate (E211)

Citric acid monohydrate

Sodium citrate

Saccharin sodium

Glycerol

Sucrose

Raspberry flavour including propylene glycol (E1520), glyceryl triacetate (E1518), triethyl citrate (E 1505), flavouring substances, flavouring preparations

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 35 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

200 ml amber glass bottle with a child-resistant cap and a polypropylene 20ml measuring cup graduated from 2.5 ml to 15 ml.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Pharma UK Limited

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WD18 9SS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0318

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/07/2025

10 DATE OF REVISION OF THE TEXT

25/02/2026