SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethosuximide Aristo 250 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 250 mg ethosuximide.

Excipients with known effect
Each soft capsule contains 3.4 mg - 9.9 mg sorbitol (E 420).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

Oval, yellow opaque soft capsules, size 6

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ethosuximide gives selective control of absence seizures (petit mal) even when complicated by grand mal.
It is also indicated for myoclonic seizures

4.2 Posology and method of administration

Posology

Adults, the elderly and paediatric population over 6 years of age
Start with a small dose - 500 mg daily with increments of 250 mg every five to seven days until control is achieved with 1000-1500 mg daily. Occasionally, 2000 mg, in divided doses may be required.

Paediatric population aged 0-6 years
Children aged 0-6 years old and those who are unable to swallow capsules should be given ethosuximide oral liquid.

Effective plasma levels of ethosuximide normally lie between 40 and 100 μg/ml but the clinical response should be the criteria for the regulation of the dosage. The half-life of ethosuximide in plasma is more than 24 hours but the daily dose if large, is more comfortably divided between morning and evening.

Currently available clinical trial data regarding the use of ethosuximide in the paediatric population are described in section 5.1.

Method of administration
Ethosuximide Aristo is for oral use.
The soft capsules can be taken during or after meals with some liquid.

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

General
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs (AEDs) 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. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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.

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 medulla injury. 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.

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.

Ethosuximide Aristo contains sorbitol (E 420)
Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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. The prescribing physician should weigh the benefit versus risk of ethosuximide in treating or counselling epileptic women of childbearing potential.

Breast-feeding

Ethosuximide is excreted into 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. Breast feeding is best avoided.

4.7 Effects on ability to drive and use machines

Ethosuximide 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

Frequencies reported are as follows:
Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < /100); Rare (≥ 1/10,000 to < 1/1,000); Not known (frequency cannot be estimated from the available data)

* AE frequency estimated from post-marketing safety database

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 disorders
Uncommon: Haematuria*

Reproductive system and breast disorders
Uncommon: Vaginal haemorrhage*

General disorders and administration site conditions
Uncommon: Fatigue, irritability*

Investigations
Uncommon: Weight decreased

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.

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 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

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 the stomach should be emptied, respiration maintained, and any other symptoms treated accordingly. Activated charcoal and purgatives are known to be

used in the treatment of overdosage. Haemodialysis may be useful. Forced diuresis and exchange transfusions are ineffective.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, succinimide derivatives
ATC code: N03AD01

Mechanism of action
The reduction of seizure frequency is thought to be achieved by depression of the motor cortex and elevation of the threshold to convulsive stimuli as seen by the suppression of the characteristic spike and wave EEG pattern.

Pharmacodynamic effects
Ethosuximide gives selective control of absence seizures (petit mal) even when complicated by grand mal. It is also indicated for myoclonic seizures. Compared to other anti-convulsants, ethosuximide is more specific for pure petit mal.

Paediatric population
In a double-blind, randomised trial of 20 weeks duration in 453 children aged 2.5 to 13 years old with newly diagnosed childhood absence epilepsy, the efficacy, tolerability and neuropsychological effects of ethosuximide, valproic acid and lamotrigine as monotherapy in childhood absence epilepsy were investigated. 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 approx. 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 extensively 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.

Children and adolescents

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 carcinogenic 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

Macrogol 300
Gelatin
Glycerol
Sorbitol liquid, partially dehydrated
Water, purified
Titanium dioxide (E 171)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

PVC/PVdC//Al blister

50 soft capsules
56 soft capsules
100 soft capsules
200 soft capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH

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8 MARKETING AUTHORISATION NUMBER(S)

PL 40546/0044

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