SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethosuximide Accord 250 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg ethosuximide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft.

Transparent oval soft gelatin capsules containing clear oily liquid and bearing the designation "05" on one side of the capsules. Capsule dimensions are approx. 14 x 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ethosuximide Accord 250 mg soft capsules give selective control of absence seizures (petit mal) even when complicated by grand mal.

They are also indicated for myoclonic seizures.

4.2 Posology and method of administration

Adults, elderly and children over 6 years

Start with a small dose – 500 mg daily with increments of 250 mg every five to seven days, depending on the patient's tolerance until control is achieved with 1000–1500 mg daily. Occasionally 2000 mg in divided doses may be necessary.

Children between 0-6 years

Children aged 0-6 years old and those who are unable to swallow capsules should be given ethosuximide oral liquid. Currently available clinical trial data regarding the use of ethosuximide in the paediatric population are described in section 5.1.

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

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.

Use with caution in hepatic or renal impairment. Monitor liver/renal function and ethosuximide concentrations.

Method of administration

Ethosuximide Accord 250 mg soft capsules are for oral use.

The 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.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

Suicidal ideation and behaviour has been reported to occur in patients treated with anticonvulsants in various indications. A meta-analysis of randomised placebo-controlled studies with anticonvulsants also reveals a slight increase in the risk of suicidal ideation and behaviour. The mechanism behind this risk is not known and the available data do not exclude the possibility of an increased risk for ethosuximide.

Patients must therefore be closely monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and their carers) must be advised that, if signs of suicidal ideation or behaviour occur, medical advice must be sought.

In patients with combined forms of epilepsy, ethosuximide can induce generalised seizures. When switching from existing medication to ethosuximide or when discontinuing ethosuximide, this should be done gradually.

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

Ethosuximide Accord 250 mg soft capsules should always be withdrawn slowly.

Regular monitoring of the blood count is recommended, especially in patients with hepatic or renal dysfunction, as bone marrow depression and thrombocytopenia may occur (including some cases with fatal outcome). Periodic blood tests should be performed.

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.

In patients with a history of psychiatric illness in particular, corresponding psychiatric undesirable effects can occur (see section 4.8, paranoid/hallucinatory symptoms,

anxiety states, agitation), and therefore special caution must be exercised when ethosuximide is used in this group of patients.

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

If ethosuximide is administered in combination with other anticonvulsants, the dosage of ethosuximide and/or other anticonvulsants should be adjusted, depending on the patient's response. Ethosuximide interacts with other anticonvulsants such as phenytoin and valproic acid. It is recommended that serum concentrations of the individual substances be regularly determined. Valproic acid can increase the plasma concentration of ethosuximide in the majority of patients.

Effect of ethosuximide on other medicinal products
As a rule, ethosuximide does not change the plasma concentrations of other anti-epileptics such as primidone, phenobarbital and phenytoin, because ethosuximide is not an enzyme inducer. However, in isolated cases, a rise in phenytoin concentration has been reported when ethosuximide was administered concomitantly.

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

Concomitant use of ethosuximide and alcohol or substances with sedative properties should be avoided in order to prevent CNS depression.

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

Ethosuximide crosses the placenta. There are insufficient data on the use of ethosuximide in human pregnancy to assess the potential harm. Congenital abnormalities are known to occur more frequently in newborn infants of mothers using anticonvulsant agents than in other infants. The most frequently reported malformations are cleft lip, cardiovascular malformations and neural tube defects. The likelihood of harmful effects occurring in the unborn foetus appears to be greater in combination with other anticonvulsant agents. Ethosuximide has been shown to be harmful in animal trials.

In general, it is not desirable to discontinue anticonvulsant therapy during pregnancy. Where possible, preference should be given to monotherapy during pregnancy.

Patients must be informed of the increased risk of malformations and made aware of the option of prenatal screening. Between day 20 and day 40 of the pregnancy in particular, the lowest, yet still effective, ethosuximide doses must be given and plasma concentrations must be monitored.

Some anticonvulsant agents may cause folic acid deficiency. Moreover, folic acid supplementation at doses customary for all pregnant women is strongly recommended. To avoid bleeding complications in the newborn infant due to possible vitamin K deficiency, which has been reported after maternal use of some anticonvulsant agents, consideration can be given to administering vitamin K to the mother in the last weeks of pregnancy. For the newborn infant, parenteral administration of vitamin K is advised immediately postpartum.

Breast-feeding

Ethosuximide is excreted in human milk in such quantities that subtherapeutic concentrations may occur in the infant. Concentrations in human milk of up to 94% of the maternal serum concentration have been reached. Adverse reactions may occur in the infant, such as irritability, poor sucking reflex and drowsiness. Breast-feeding is therefore not recommended during treatment with ethosuximide.

Fertility

There are no data on the effects of Ethosuximide Accord 250 mg soft capsules on male or female fertility.

4.7 Effects on ability to drive and use machines

Ethosuximide can impair a patient's reactivity and ability to react speedily and may cause side effects such as drowsiness or dizziness.

Therefore, during any adjustment phase, including higher doses or in combination with other medicinal products affecting the central nervous system, the ability to drive or operate machines safely may be 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

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)

Undesirable effects in the therapeutic dose range are common and are observed in approximately 1 in 6 patients. The majority involve nausea, vomiting, singultus and abdominal pain.

Blood and lymphatic system disorders	
Rare	Leukocytopenia*, thrombocytopenia*, agranulocytosis*, eosinophilia*
Not known	Aplastic anaemia*, pancytopenia*, neutrophilia and monocytosis have been reported
Immune system disorders	
Rare	Nephrotic syndrome
Metabolism and nutrition disorders	
Uncommon	Weight loss, appetite disturbances
Psychiatric disorders	
Uncommon	Social withdrawal, anxiety, sleep disturbances
Rare	Paranoid/hallucinatory manifestations developing within days or weeks
Not known	Psychological changes (psychoses), states of agitation, depression, increased libido
Nervous system disorders	
Uncommon	Severe headache, ataxia, lethargy
Not known	Euphoria, dyskinesia, photophobia, dizziness**, drowsiness, behavioural disorders, fatigue, hyperactivity
Respiratory, thoracic and mediastinal disorders	
Common to very common	Singultus
Eye disorders	
Not known	Myopia
Gastrointestinal disorders	
Common to very common	Nausea, vomiting*, abdominal pain
Uncommon	Diarrhoea, constipation
Skin and subcutaneous tissue disorders	
Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Rare	Skin rash, erythema nodosum, Stevens-Johnson syndrome
Reproductive system and breast disorders	
Not known	Vaginal bleeding
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus (SLE)
General disorders and administration site conditions	
Not known	Irritability, night terrors, inability to concentrate, aggressiveness

* effect independent of dose (see also section 4.4).

**In combined forms of epilepsy and also in combination with other anticonvulsant agents, 20- 30% experienced nausea, vomiting, headache, dizziness.

In most cases of leucopenia the blood picture has returned to normal on reduction of

dose or discontinuation. In some instances, patients who become leucopenic on other anticonvulsant therapy have been satisfactorily treated with ethosuximide alone.

Patients should be advised to seek immediate medical attention for full blood count tests if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding develop.

Ethosuximide when used alone in mixed types of epilepsy may increase the frequency of generalised tonic-clonic (grand mal) seizures in some patients.

Psychotic states thought to be induced or exacerbated by anticonvulsant therapy have been reported.

Lupus like reactions have occasionally been reported in children given ethosuximide, varying from severe systemic immunological disorders, e.g. the nephrotic syndrome generally with complete recovery on drug withdrawal, to the detection of antinuclear antibodies without clinical features.

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).

As a rule, adverse reactions resolve when the dosage is reduced. Usually, they do not recur upon subsequent dose escalation.

In the event of undesirable effects that are reversible and not dose-dependent, discontinuation of ethosuximide is indicated. They may be expected to recur on rechallenge. Impairment of performance is possible during long-term therapy, e.g. a reduction in academic achievement in 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: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
When assessing any intoxication, the possibility of multiple agent intoxication must also be considered, e.g. as a result of taking several drugs with suicidal intent. The symptoms of an overdose are potentiated by alcohol and other agents with a central depressant effect.
Ethosuximide may cause nausea, vomiting, headache, dizziness, anorexia, ataxia, tremor, (motor) restlessness, choreiform movements, CNS depression (leading to coma), hypotension and respiratory depression. Due to the long half-life, effects can persist for a long time. Hepatic and renal damage may also occur. Idiosyncratic reactions may consist of skin rash, erythema, blood dyscrasias, allergic reactions, systemic lupus erythematosus, behavioural changes and psychoses.
If intoxication is suspected, determination of the plasma concentration of the anti-epileptic agent is always recommended.

Management
Absorption may be prevented by inducing emesis or gastric lavage, followed by administration of activated charcoal (adsorbent) and sodium sulphate (laxative). Intensive care admission is indicated. Haemodialysis may be used if necessary. Further treatment should be supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, succinimide derivatives, ATC code: N03AD01

Mechanism of action
Ethosuximide is a succinimide derivative. 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.

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
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 prespecified and post hoc analyses, ethosuximide resulted in fewer attentional effects as compared with valproic acid (at week 16 and week 20, the percentage of 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 readily absorbed from the gastro-intestinal tract and extensively metabolised in the liver.

After taking 1 g ethosuximide, C_{max} values of 18-24 µg/ml were measured in 3 study subjects after 1-4 hours.

In adults receiving long-term treatment with approximately 15 mg/kg body weight a plasma concentration of approximately 50 µg/ml is reached. With an oral dose of 1

mg/kg daily, a plasma concentration of 2-3 µg/ml can be expected. Steady state can be expected to be reached 8-10 days after starting therapy. Despite major interindividual variations in plasma concentration at the same oral dose, there is a linear relationship between dose and plasma concentration.

The therapeutic plasma concentration of ethosuximide is stated as 40-100 µg/ml. Plasma concentrations above 150 µg/ml can cause toxic effects.

Paediatric population
In one study, following a single administration of 500 mg ethosuximide to children (7-8.5 years, 12.9-24.4 kg body weight), C_{max} values of 28.0-50.9 µg/ml were measured after 3-7 hours. In long-term medication with 20 mg/kg body weight, a plasma concentration of approximately 50 µg/ml is reached. With an oral dose of 1 mg/kg daily in childhood, a plasma concentration of 1-2 µg/ml can be expected. Younger children therefore need somewhat higher doses than older children.

Distribution
It is widely distributed throughout the body but is not significantly bound to plasma proteins, so saliva concentrations may be useful for monitoring. Peak serum levels occur 1 to 7 hours after single oral dose. Therapeutic levels are between 40 and 100 mcg/ml.

Biotransformation
Ethosuximide is largely metabolised oxidatively in the liver. Several metabolites are formed, primarily the two diastereomers of 2-(1-hydroxyethyl)-2-methyl-succinimide and 2-ethyl-2-methyl-3-hydroxy-succinimide. The metabolites are probably inactive.

Elimination
Only 10-20% of ethosuximide is excreted unchanged in urine. The main ethosuximide metabolites formed, the two diastereomers of 2-(1-hydroxyethyl)-2-methyl-succinimide and 2-ethyl-2-methyl-3-hydroxy-succinimide, are in part conjugated as glucuronides and excreted renally.

After a single oral administration of 13.1-18.0 mg ethosuximide/kg body weight to 12 male study subjects (20-23 years, 57.2-114.8 kg body weight) a plasma half-life of 38.3-66.6 hours was measured. With a single dose of 500 mg ethosuximide (capsules) to 5 children, plasma half-lives of 25.7-35.9 hours were measured and of 24.8-41.7 hours when administered as solution.

Passage into breast milk
Ethosuximide passes into breast milk. The ratio of ethosuximide concentration in breast milk to that in plasma is stated as 0.94 ± 0.06.

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

Capsule contents:
Macrogol 400
Water, purified

Capsule shell:
Gelatin
Glycerol
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening of the HDPE bottle: 60 days.

6.4 Special precautions for storage

Store below 30°C.

HDPE bottle: Keep the bottle tightly closed.

6.5 Nature and contents of container

PVC/PVdC-Aluminium blisters containing 56 capsules in a carton and/or HDPE bottles containing 56 capsules in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1300

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/04/2024

10 DATE OF REVISION OF THE TEXT

23/08/2024