SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethosuximide Tillomed 250 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 250 mg ethosuximide.

Excipients with known effect:

Each soft capsule contains: Sorbitol 17.43 mg

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

Transparent clear, oblong, soft gelatin capsule filled with clear liquid. Imprinted with "HP 532" with White ink

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ethosuximide Tillomed 250 mg soft capsules, give 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, 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 to 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 Tillomed 250 mg soft capsules is for oral use.

The capsules can be taken during or after meals with some liquid.

4.3 Contraindications

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

Patient 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 dyskinesia occurs (see section 4.8), ethosuximide must be discontinued and diphenhydramine may be administered, if required.

Ethosuximide Tillomed 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.

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.

Excipients with known effects:

This medicine contains 17.43 mg sorbitol per capsule.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

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.

The plasma concentrations of ethosuximide may be reduced by carbamazepine, primidone, phenobarbital 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

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 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. 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. 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 250 mg capsules, soft 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

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 with ethosuximide treatment (see section 4.4).
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 < 1/1000)
Very rare (<1/10,000)
Not known (frequency cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						Peripheral blood count abnormalities (slight decrease in leukocytes). Aplastic anaemia, agranulocytosis, pancytopenia, neutrophilia, Monocytosis, eosinophilia and leukopenia have been reported, thrombocytopenia

Immune system disorders				Nephrotic syndrome		
Psychiatric disorders						Psychological changes (psychoses), states of agitation, depression, paranoid psychoses, sleep disturbances, increased libido
Nervous system disorders						Apathy, euphoria, ataxia, dyskinesia, photophobia, headache*, dizziness*, drowsiness, anorexia, behavioural disorders, fatigue, hyperactivity
Eye disorders						Myopia
Gastrointestinal disorders						Nausea, vomiting*, diarrhoea, abdominal pain, gum hypertrophy, swelling of the tongue
Skin and subcutaneous tissue disorders				Skin rash, erythema nodosum, Stevens-Johnson syndrome		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders				Systemic lupus erythematosus (SLE)		
Reproductive system and breast disorders						Vaginal bleeding

General disorders and administration site conditions					Weight loss, hiccoughs, irritability, night terrors, inability to concentrate, aggressiveness

*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.

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

Symptoms

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.

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: Anticonvulsants, 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, randomized 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 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.

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. It has a long elimination half life: adults 40 - 60 hours; children 30 hours.

Elimination

It is excreted in the urine mainly in the form of its metabolites.

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

Gelatin,
Glycerol,
Sorbitol (E420),
Macrogol 400
Purified water

Printing ink containing:
Shellac glaze ~45% (E904)
Titanium Dioxide (E171)
Isopropyl Alcohol
Propylene Glycol (E 1520)
N-Butyl Alcohol
Ammonium Hydroxide 28% (E527)
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- HDPE Bottle pack with white round plastic (polypropylene) child resistant closure (CRC) cap with liner.

  Pack sizes: 56’s, 100’s, 200’s Capsules
- PVC/PVDC/Alu Blister Pack in Carton.

  Pack sizes: 56’s capsules

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 for cytotoxic medicinal products.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited
220 Butterfield
Great Marlings, Luton
LU2 8DL, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0682

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/01/2024

10 DATE OF REVISION OF THE TEXT

09/07/2024