1.3.1 SUMMARY OF THE PRODUCT PROPERTIES

1. NAME OF THE MEDICINE

Ethymal 125 mg, capsules, soft
Ethymal 250 mg, capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The capsules contain 125 and 250 mg ethosuximide respectively. See section 6.1 for the complete list of auxiliary substances.

3. DOSAGE FORM

Capsule, soft

4. CLINICAL DETAILS

4.1 Therapeutic indications

Absences (petit mal)

4.2 Dosage and administration

Dosage

The dosage should be determined individually, based on the serum level.

Children above 6 years and adults

Start with 250 mg twice a day.

In case of outpatient treatment, the daily dosage can be increased every 7 days and in case of clinical treatment every 4 days with 125 mg, until the optimal dosage is reached. Usually, this will not exceed an amount of 1500-2000 mg per day (1000 mg below 6 years).

Paediatric patients

Children under 3 years

Initially 10 mg/kg of body weight per day in 1-2 doses. Maintenance dose: 20-40 mg/kg of body weight per day in 1-2 doses.

Children between 3 and 6 years

Start with 125 mg twice a day.
If the prescribed dosage is not manageable due to the intensity of capsules and the weight of the child, we recommend the use of the syrup.

**Administration**
The capsules can be administered with water, if preferred.

### 4.3 Contraindications

Hypersensitivity to the active substance ethosuximide or other succinimides or to (one of) the auxiliary substance(s) mentioned under section 6.1.

### 4.4 Special warnings and precautions for use

The occurrence of suicidal ideation and behaviour has been reported from patients that were treated with anti-epileptic medication for various indications. A meta-analysis of randomized, placebo-controlled trials with anti-epileptic medication also shows a small increase of the risk of suicidal ideation and behaviour. The mechanism behind this risk is unknown and the available data does not exclude the possibility of an increased risk for ethymal.

Therefore, patients ought to be checked thoroughly for signs of suicidal ideation and behaviour and an appropriate treatment needs to be considered. It should be pointed out to patients (and their caregivers) that medical advice needs to be obtained if there are any signs of suicidal ideation or behaviour.

For patients with combined forms of epilepsy, ethosuximide can provoke generalised seizures. Both changing from existing medication to ethosuximide and terminating ethosuximide need to be done gradually. It is recommended to check the blood count regularly, especially when patients have a hepatic or renal disease, bone marrow suppression and thrombocytopenia (including some cases with fatal outcome). Blood should be tested periodically.

### 4.5 Interactions with other medication and other forms of interaction

If ethymal is administered in combination with other anti-epileptic medication, the dosage of ethosuximide and/or other anti-epileptic medication should be adjusted, depending on the reaction of the patient. Ethosuximide interacts with other anti-epileptic medication, like phenytoin and valproic acid. Regular definition of the serum concentrations of the separate substances is recommended. Isoniazid can increase the blood level of ethosuximide. Simultaneous use of ethymal and alcohol or substances with sedative properties should be avoided in order to prevent depression of the CNS.

### 4.6 Pregnancy and breastfeeding

**Pregnancy**

There is insufficient data on the use of ethosuximide during pregnancy to assess the possible harmfulness. It is known that babies whose mothers use anti-epileptic medication show congenital abnormalities more often than other infants. The chance of harmful effects occurring for the embryo and foetus seems greater in combination with other anti-epileptic medication. In vivisection, ethosuximide appeared to be harmful.
In general, it is not recommended to terminate an anticonvulsive therapy during pregnancy. If possible during pregnancy, priority should be given to monotherapy. The last doses of ethosuximide that are still effective should be administered and the plasma concentrations should be checked.

Certain anti-epileptic medication possibly causes a folic acid deficiency. For that matter, folic acid supplements are highly recommended, in usual dosages for every pregnant woman. In order to prevent the baby from getting bleeding complications due to a possible vitamin K deficiency – reported after maternal use of certain anti-epileptic medication – it could be considered to give the mother vitamin K in the last weeks of the pregnancy. For the baby, parenteral administration of vitamin K directly postpartum is advised.

Breastfeeding
The amount of ethosuximide passing into the breastmilk is so high that the baby can get sub-therapeutic concentrations. The baby could experience irritability, trouble with drinking and sleepiness. Therefore, breastfeeding during treatment with ethosuximide is discouraged.

4.7 Effects on the ability to drive and operate machinery

Please be aware that this medication can decrease reactivity in traffic and operation of dangerous machinery.

4.8 Side effects

Gastrointestinal complaints, headache, dizziness, sleepiness, behaviour disorders, mental changes (or even psychoses). In rare cases, deviations of the peripheral blood count (light temporary albuminuria, minor decrease of leukocytes).

In case of combined forms of epilepsy, as well as in combination with other anti-epileptic medication, nausea, vomiting, headache and dizziness were reported in 20/30% of the cases and, in a small number of cases, a state of excitement and episodic psychoses. As a rule, the side effects disappear when the dosage is decreased. Usually, they will not reappear when the dosage is increased again.

In rare cases, aplastic anaemia, agranulocytosis, pancytopenia, eosinophilia and leukopenia have been reported. Systemic lupus erythematosus (SLE) and Steven Johnson syndromes are reported under ethosuximide. Side effects that call for a decrease of the dosage would occur when levels rise above 160 µg/ml.

Reports of possible side effects
It is important that you report any side effects after administration of the medicine. This way, the ratio between advantages and risks of the medicine can be monitored constantly. Professionals in medical healthcare are requested to report all possible side effects via the Nederlands Bijwerkingen Centrum Lareb. [Dutch Pharmacovigilance Centre Lareb]. Website: www.lareb.nl.

4.9 Overdosage

Symptoms can consist of nausea, dizziness, anorexia, ataxia, tremors, (motor) agitation, choreiform movements, CNS depression (leading to coma), hypotension and respiratory depression. Due to the long half-life, the effect can linger for a long time. In addition, hepatic or renal diseases can occur. Idiosyncratic reactions can consist of rash, erythema, blood dyscrasias, allergic reactions, systemic lupus erythematosus, changes in behaviour and psychoses.
Absorption can be prevented by stimulating vomiting or gastric lavage, followed by administration of activated carbon (adsorbent) and sodium sulphate (laxative). The patient has to be admitted to intensive care. If necessary, haemodialysis can be applied. Further treatment needs to be supportive and symptomatic.

5. PHARMAACOLOGICAL PROPERTIES

5.1 Pharmacodynamical properties

Pharmacotherapeutic category: anti-epileptic medication, ATC code: N03AD01

Ethosuximide is a succinimide-derivative. It only works with absences. The mechanism of action is unclear. Normal therapeutic plasma levels are expected to lie between 40 and 80 µg/ml. There are considerable individual variations. Maximum therapeutic levels of 220 µg/ml in complicated cases are described.

5.2 Pharmacokinetic properties

The resorption is complete. The maximum in the blood level is reached after 1 to 7 hours. There is hardly any protein binding. The liquor level equals the plasma level, as well as the concentration in the breastmilk. The half-life is approximately 60 hours, for children approximately 30 hours. Both metabolites (hydroxylated) and the unchanged ethosuximide (approximately 10-20% of a dose) are excreted with the urine.

5.3 Data from the preclinical safety investigation

No particulars.

6. PHARMACEUTIC DATA

6.1 List of auxiliary substances

Macrogol 300
gelatine
glycerol (E422)
partially dehydrated sorbitol
hydrochloric acid (E507).

In addition, the capsules of 250 mg contain iron oxide red (E172) and titanium dioxide (E171).

6.2 Incompatibilities
Not applicable.

6.3 **Shelf-life**

3 years.

6.4 **Special precautions for storage**

Store the capsules in their original packaging in a dry place, below 25°C.

6.5 **Type and contents of the packaging**

The capsules are available in Al/PVC/PE/PVDC blister foil packages of 50 pieces and in vial packaging of 100 pieces. In addition, the capsules are also available in EAV. Not all mentioned packaging sizes are available in store.

6.6 **Special precautions for removal and other instructions**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

8. **NUMBER(S) OF THE MARKETING AUTHORISATION**

RVG 05634    Ethymal 125 mg, capsules, soft
RVG 02982    Ethymal 250 mg, capsules, soft

9. **DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

RVG 05634    registered 11 September 1968
RVG 02982    registered 15 December 1967

10. **DATE OF REVISION OF THE TEXT**

Last alteration concerns the lay-out: 26 February 2014