1. **Trade name of the medicinal products**
   Petnidan®
   Petnidan® Syrup

   Active constituent: ethosuximide

2. **Prescription status/legal category**
   Prescription-only medicines

3. **Composition of the medicinal products**

3.1 **Chemical and pharmacological group**
   Succinimide, antiepileptic

3.2 **Ingredients, qualitative and active ingredients, qualitative and quantitative**

   - **active ingredients**
   1 capsule Petnidan® contains
   250 mg ethosuximide.

   5 ml solution (1 measuring spoon) Petnidan® syrup contain
   250 mg ethosuximide.

   - **other ingredients**
   *Petnidan®*
   iron oxide (E172), gelatin, glycerol, mannitol, macrogol, sorbitan, sorbitol, titanium
dioxide (E171);

   *Petnidan® Syrup*
   flavouring, citric acid (E330), hypromellose, methyl-4-hydroxybenzoate sodium salt (E219), polyglycol, saccharin sodium, purified water.

4. **Therapeutic indications**
   - pyknoepileptic absences as well as complex and atypical absences.
   
   Note:
   In order to prevent grand mal seizures often associated with complex and atypical absences, ethosuximide can be used in conjunction with other effective antiepileptics (e.g. primidone, phenobarbitone). Concomitant prophylaxis of grand mal seizures may only be omitted in the treatment of pyknoepileptic absences in children of school age.

   - myoclonic-astatic petit mal.
   - adolescent myoclonic seizures (impulsive petit mal).

5. **Contraindications**
   Ethosuximide is absolutely contraindicated in known hypersensitivity to ethosuximide, other succinimides or other constituents of the medical product (see Point 3.2).

   **Use during pregnancy and lactation**
   (see Point 14)

6. **Adverse reactions**
Adverse reactions are common in the therapeutic dose range and are observed in around 1/6 of patients. The majority present as nausea, vomiting, singultus (hiccups) and abdominal pain, occasionally as lethargy, withdrawal, occasionally as severe headache, sleep and appetite disturbances, weight loss, diarrhoea, obstipation or ataxia and anxiety. In rare cases paranoid hallucinatory phenomena may develop within days or weeks. In a few isolated cases there have been reports of dyskinesia developing within the first 12 hours of treatment which, however, disappeared following discontinuation of ethosuximide or resolved rapidly on administration of diphenhydramine.

Dose-independent side effects may include allergic skin reactions such as exanthema, although more severe systemic forms such as Stevens-Johnson syndrome are also possible. Eosinophilia has been observed. Lupus erythematosus of varying severity has occurred rarely. Leucopenia and agranulocytosis have been reported rarely and there have been isolated reports of aplastic anaemia and pancytopenia.

**Special precautions for use**

The likelihood of dose-dependent side effects can be reduced by careful dosing (gradual start of therapy, slow incremental dosage) and taking ethosuximide during or after meals.

If dyskinesias occur, (see Adverse reactions) ethosuximide treatment should be stopped; if necessary, intravenous diphenhydramine may be indicated.

Corresponding psychological side effects (paranoid hallucinatory symptoms, anxiety, agitation) are particularly likely to occur in patients with a history of psychiatric disorders. Ethosuximide must be prescribed with particular caution in this patient group.

Patients must be closely monitored for clinical symptoms of bone marrow damage (fever, sore throat, haemorrhage). Regular blood counts are recommended (at first monthly, after 1 year every 6 months) in order to detect possible bone marrow damage. It appears advisable to reduce the ethosuximide dosage or discontinue therapy if the leucocyte count falls below 3500/mm³ or the granulocyte fraction is less than 25%.

Ethosuximide should be discontinued if reversible dose-independent side effects occur. The effects are likely to recur following renewed administration.

On account of the content of alkyl-4-hydroxybenzoates (parabens) in Petnidan® Syrup, hypersensitivity reactions may occur in predisposed patients.

7. **Interactions with other drugs**

Special attention must be paid to the following interactions between ethosuximide and other drugs:

Concomitant administration of ethosuximide and centrally-acting drugs, alcohol or substances that provoke seizures must be avoided.

In general, ethosuximide does not affect the plasma concentrations of other antiepileptics (e.g. primidone, phenobarbitone, phenytoin), since ethosuximide is not an enzyme inducer. However, there have been isolated reports of an increased plasma phenytoin concentration when ethosuximide is given concomitantly.

Simultaneous administration of carbamazepine enhances the plasma clearance of ethosuximide.

Concurrent administration of valproic acid may increase the serum concentration of ethosuximide in the majority of patients.

8. **Warnings**

None.

9. **Most important incompatibilities**

None known.

10. **Posology with individual and total daily doses**
The ethosuximide dosage is adapted to the individual clinical picture, the clinical response and individual tolerability. Initiation of therapy is gradual with incremental dosage. The initial total daily dose for children and adults is 5 - 10 mg ethosuximide/kg body weight. The daily dose can be increased by 5 mg ethosuximide/kg body weight at intervals of 4 - 7 days (depending on when steady state is reached: 8-10 days).

The daily maintenance dose is generally 20 mg/kg body weight in children and 15 mg/kg body weight in adults. The total daily dose should not exceed 40 mg/kg body weight in children and 30 mg/kg body weight in adults.

The following dosage is recommended for patients without previous treatment:

Mean daily dosage in mg divided into 2 single doses (morning and evening)

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Infants and children up to 2 years*</th>
<th>Children 2 - 5 years*</th>
<th>Children 6 - 9 years*</th>
<th>Children over 9 years and adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 - 3</td>
<td>-</td>
<td>125</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Days 4 - 7</td>
<td>-</td>
<td>250</td>
<td>250</td>
<td>375</td>
</tr>
<tr>
<td>Week 2</td>
<td>125</td>
<td>250</td>
<td>250</td>
<td>375</td>
</tr>
<tr>
<td>Week 3</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>From week 4</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>mean maintenance</td>
<td>20 mg/kg body weight</td>
<td>500 - 1000</td>
<td>500 - 1000</td>
<td>1000 - 2000</td>
</tr>
<tr>
<td>dosage (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*) Infants and young children should be treated with Petnidan® Syrup. The measuring spoon can be used for both 250 mg (5 ml) and 125 mg (2.5 ml).

Ethosuximide is dialysable. Haemodialysis patients therefore need an additional dose or a changed dosage plan. During four hours of dialysis 39 to 52 % of the administered dose is removed.

11. Method and duration of administration

The daily dose may be given as a single dose or divided into 2 or 3 doses. Medication should be taken during or after meals. The capsules may be taken with a little fluid. Petnidan® Syrup may also be taken with meals (e.g. stirred into baby food).

Antiepileptic therapy is always long-term treatment. In every case, dose adjustment, duration of treatment and when to stop treatment with Petnidan® must be decided by a specialist (neurologist, neuropaediatrician) on an individual basis.

In general the dosage may only be reduced and medication withdrawn after the patient has been free of seizures for at least 2 - 3 years.

Medication must be withdrawn gradually over a period of one to two years. Children may be allowed to grow out of the dose per kg body weight instead of adjusting the dose in accordance with their age, whereby EEG findings must not deteriorate.

12. Emergency measures, symptoms and antidotes

In every case of intoxication, the possibility of multiple poisoning through the potential ingestion of several drugs, for example with suicidal intent, must be considered.

a) Symptoms of intoxication

Ethosuximide has low toxicity. Overdose leads to an exaggeration of the side effects listed under “Adverse reactions” such as tiredness, lethargy, depressed moods and agitation, occasionally irritability.
In cases of suspected intoxication it is advisable to measure plasma concentrations of the antiepileptic drugs.

b) Management of intoxication
Severe overdose should be treated by initial gastric irrigation and subsequent administration of activated charcoal in addition to intensive medical monitoring of the cardiovascular system and respiration. There is no known specific antidote.

13. Pharmacological and toxicological properties, pharmacokinetics and bioavailability, in so far as this information is relevant for therapeutic use

13.1 Pharmacological properties
Ethosuximide is a succinimide antiepileptic agent. Its mode of action is not fully understood; an inhibitory effect on the breakdown of GABA has been reported.

13.2 Toxicological properties
a) Acute toxicity
Plasma concentrations over 150 µg/ml may have toxic effects (see also Point 12). The LD50 in mice is 1400 - 1550 mg/kg body weight.

b) Chronic toxicity
Six months administration of up to 1200 mg/kg daily was well tolerated in mice. Dogs tolerated 12.5 - 50 mg/kg body weight twice daily for over a year.

13.3 Pharmacokinetics

Absorption, plasma levels
An oral dose of ethosuximide is almost completely absorbed. In three volunteers given an oral dose of 1 g ethosuximide Cmax values of 18 - 24 µg/ml were measured after 1 - 4 hours. In another study in children (7 - 8.5 years old, 12.9 - 24.4 kg body weight) with a single oral dose of 500 mg ethosuximide Cmax values of 28.0 - 50.9 µg/ml were recorded after 3 - 7 hours.

A plasma concentration of approximately 50 µg/ml in children is obtained under long-term medication with 20 mg/kg body weight. A lower dose (approximately 15 mg/kg body weight) is sufficient to achieve the same plasma concentrations in adults. Steady state levels may be expected 8 - 10 days after beginning therapy. Despite wide interindividual variations in plasma concentrations at the same oral dose, the plasma concentration increases linearly with the dose. An oral dose of 1 mg/kg daily may be expected to achieve a plasma concentration of 2 - 3 µg/m/1 or 1 - 2 µg/ml in children. Thus younger children require a slightly higher dosage than older children. The therapeutic plasma concentrations of ethosuximide range between 40 - 100 µg/ml. Plasma concentrations in excess of 150 µg/ml can cause toxic effects.

Distribution/plasma protein binding
Ethosuximide is not bound to plasma proteins. The concentration of ethosuximide in cerebrospinal fluid and saliva is equivalent to that found in plasma. The apparent volume of distribution is approximately 0.7 l/kg body weight.

Ethosuximide crosses the placenta.
*Excretion into breast milk*
Ethosuximide is excreted into breast milk. The proportion of the ethosuximide concentration in breast milk to the plasma concentration has been reported as 0.94 ± 0.06.

*Metabolism/excretion*
Ethosuximide undergoes extensive oxidation in the liver; only 10 - 20% is excreted in the urine in unchanged form. Several metabolites are produced, predominantly the two diastereomeric forms of 2-(1-hydroxyethyl)-2-methylsucinimide and 2-ethyl-2-methyl-3-hydroxysuccinimide. The two metabolites are probably pharmacologically inactive and are excreted partly in the urine as glucuronide conjugates.

In 12 male volunteers a plasma half-life of 38.3 - 66.6 hours was measured following a single oral dose of 13.1 - 18.0 mg ethosuximide/kg body weight (20 - 23 years of age, 57.2 - 114.8 kg body weight). In five children plasma half-lives of 25.7 - 35.9 hours for capsules and 24.8 - 41.7 hours for syrup were measured after a single oral dose of 500 mg ethosuximide.
13.4 **Bioavailability**

A study carried out in 1991 with Petnidan® capsules and Petnidan® syrup (500 mg ethosuximide) with 14 male volunteers (aged between 23 and 35 years, body weight 64 to 80 kg) revealed the following data:

See diagram.

(Plasma concentration (µg/ml), Reference product, Time (h))

The curves show the mean ethosuximide plasma concentration following a single dose of 500 mg (2 Petnidan® capsules or 2 measuring spoons of Petnidan® syrup) in 14 healthy individuals.

**Pharmacokinetic parameters of Petnidan® and Petnidan® syrup after an oral dose of 500 mg.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Petnidan® capsules</th>
<th>Petnidan® syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax [mg/l]</td>
<td>10.8 ± 2.0</td>
<td>10.1 ± 1.7</td>
</tr>
<tr>
<td>AUC0-∞ [mg/l·h]</td>
<td>708.1 ± 126.3</td>
<td>655.7 ± 151.4</td>
</tr>
<tr>
<td>t½ [h]</td>
<td>55.2 ± 11.2</td>
<td>57.6 ± 12.0</td>
</tr>
<tr>
<td>tmax [h]</td>
<td>1.6 ± 3.6</td>
<td>1.1 ± 1.3</td>
</tr>
</tbody>
</table>

Results expressed as mean ± standard deviation

Petnidan® capsules and Petnidan® syrup are bioequivalent with respect to the amount and rate of absorption.

14. **Other precautions**

As with all antiepileptic agents it is advisable to monitor the blood count and biochemical values, especially if clinical anomalies develop (see Point 6 “Special precautions for use”).

**Use during pregnancy and lactation**

No specific embryopathy has been reported in children whose mothers are receiving ethosuximide as monotherapy. The risk of abnormality is increased in association with antiepileptic therapy. Every type of combination therapy further increases this risk, so that monotherapy is recommended during pregnancy.

Particularly between the 20th and 40th days of pregnancy, the lowest possible effective dose should be given. Ethosuximide serum concentrations should be regularly checked in pregnant women.

During the last month of pregnancy a vitamin K₁ product should be given to prevent haemorrhage.

Lactation must be avoided during treatment with Petnidan® as up to 94% of the maternal serum concentration may be reached in the breast milk.

The attending physician should advise women of childbearing age to inform them immediately if pregnancy occurs during Petnidan® therapy.

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**Effects on driving and use of machinery**
During the initial phase, at higher dosages and in combination with centrally-acting drugs, ethosuximide can so influence responsiveness that the ability to drive a vehicle or operate machinery is impaired. This may also occur when ethosuximide is used correctly. This effect is more pronounced in combination with alcohol. Therefore, patients should avoid driving, operating machinery or participating in any other dangerous activities at least during the adjustment phase. The attending physician must decide on a case-to-case basis taking into account the individual response and individual dosage.

This medicine is sold subject to interim legal regulations. Official investigations into its pharmaceutical quality, efficacy and safety have not yet been concluded.

15. Shelf-life
The shelf-life of Petnidan® capsules and Petnidan® syrup is 5 years. The products should not be used after the expiry date (see pack).

16. Special precautions for storage
Keep the container of Petnidan® capsules tightly closed!

17. Dosage forms and pack sizes
Petnidan®
Pack of 50 capsules
Pack of 100 capsules
Pack of 200 capsules
Clinic pack
Petnidan® syrup
Bottle of 250 ml solution
Clinic pack

18. Date of preparation
April 2001

19. Name or company and address of the holder of the marketing authorization
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