APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Pays: Belgique
2. Le présent acte public a été signé par: Lettelier, Josiane
3. Agissant en qualité de: Fonctionnaire
4. Est revêtu du sceau / timbre de: SPF Justice

Attesté
5. A Bruxelles
6. Le: 09/03/2015
7. Par le Service public fédéral Affaires étrangères, Commerce extérieur et Coopération au Développement
8. Sous le no: 9805150309934051
9. Sceau/timbre:

Signature: Jan Van de Velde

SUMMARY OF PRODUCT CHARACTERISTICS

Drugs for Mental Disorders - 2010/0019/NL
Nootropil

Expiry Date: 31/05/2012

Certified translation by Christophe Vercruysse, certified translator at the Court of First Instance of the European Communities on 11 February 2015
1. NAME OF THE MEDICINAL PRODUCT

Nootropil 800 mg film-coated tablets
Nootropil 1200 mg film-coated tablets
Nootropil 2400 mg granules for oral solution
Nootropil 20 % oral solution
Nootropil 33 % oral solution
Nootropil 1 g/5 ml solution for injection
Nootropil 3 g/15 ml solution for injection
Nootropil 12 g/60 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nootropil 800 mg film-coated tablets: piracetam 800 mg
Nootropil 1200 mg film-coated tablets: piracetam 1200 mg
Nootropil 2400 mg granules for oral solution: piracetam 2400 mg/5 g
Nootropil 20 % oral solution: piracetam 200 mg/ml
Nootropil 33 % oral solution: piracetam 333.33 mg/ml
Nootropil 1 g/5 ml solution for injection: piracetam 1 g/5 ml
Nootropil 3 g/15 ml solution for injection: piracetam 3 g/15 ml
Nootropil 12 g/60 ml solution for infusion: piracetam 12 g/60 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral forms
Nootropil 800 mg film-coated tablets
White film-coated tablets, oblong, scored and with the inscription “N/N”
Nootropil 1200 mg film-coated tablets:
White film-coated tablets, oblong, scored and with the inscription “N/N”
Nootropil 2400 mg granules for oral solution:
Cream-coloured granules
Nootropil 20 % oral solution:
Clear and colourless oral solution
Nootropil 33 % oral solution:
Clear and colourless oral solution

Injectable forms
Nootropil 1 g/5 ml solution for injection:
Clear and colourless solution for injection
Nootropil 3 g/15 ml solution for injection:
Clear and colourless solution for injection
Nootropil 12 g/60 ml solution for infusion:
Clear and colourless solution for injection

The scoring is only there to make it easier to break the tablet, it does not divide it into two equal half-doses.
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Nootropil is offered for symptomatic improvement of memory disorders or intellectual disorders in a pathological context, in the absence of a diagnosis of dementia.

- Nootropil may decrease cortical myoclonus in some patients. In order to test for sensitivity to piracetam, a trial treatment may be initiated for a limited duration.

4.2. Posology and method of administration

Posology

Memory and/or intellectual disorders:
The daily recommended dosage is 2.4 g to 4.8 g, in two or three doses.

Treatment of cortical myoclonus:
The daily recommended dosage should be started at 7.2 g while increasing by 4.8 g every three or four days, in two or three doses, up to a maximum of 24 g. Treatment with other anti-myoclonic medicines will be maintained at the same dosage regimen. Depending on the clinical benefit obtained, the doses of the other anti-myoclonic medicines will be reduced if possible.

Once started, treatment with piracetam will be continued as long as the cerebral pathology persists. In patients with an acute episode, spontaneous progress may appear over time and reduction or discontinuation of the medicinal treatment should be attempted every 6 months. This will be done by reducing the piracetam dose by 1.2 g every 2 days (every three or four days in the case of Lance-Adams syndrome to prevent sudden relapse of the disorder or a repeat of epileptic seizures related to treatment discontinuation).

Elderly

Dose adjustment is recommended in elderly patients whose renal function is compromised (see “Renal insufficiency” below). During long-term treatment, creatinine clearance should be assessed regularly to determine whether a dose adjustment is necessary.

Patients with renal insufficiency

Since Nootropil is almost exclusively eliminated by the kidneys, precautions must be taken when treating patients with renal insufficiency, and in whom the renal function should be monitored.

The half-life is increased in direct relation with the deterioration of renal function and creatinine clearance. This is also true in elderly patients, in whom creatinine excretion depends on age.

The interval between doses should be adjusted according to renal function. Refer to the table below and adjust the dose as indicated.

To use this table, it is necessary to calculate patient creatinine clearance (CLcr) in ml/min. CLcr (ml/min) may be estimated from the serum creatinine value (in mg/dl) according to the following formula:

\[
CL_{cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for women}
\]
Renal function | creatinine clearance (ml/min) | Dosage and frequency
---|---|---
Normal | >80 | Usual daily dosage divided into 2 to 4 sub-doses
Mild renal insufficiency | 50-79 | 2/3 of the usual daily dose, 2 or 3 sub-doses
Moderate renal insufficiency | 30-49 | 1/3 of the usual daily dosage, 2 sub-doses
Severe renal insufficiency | <30 | 1/6 of the usual daily dosage, 1 single dose
End stage renal disease | - | Contraindicated

Patients with hepatic insufficiency
No dose adjustment is necessary in patients with hepatic insufficiency alone. In patients with hepatic and renal insufficiency, dose adjustment is recommended (see “Patients with renal insufficiency" below).

Method of administration
The oral forms of Nootropil may be taken with or without food. The film-coated tablets will be swallowed with a little liquid. The granules will be dissolved in liquid.

The injectable form will be used when oral administration is not possible. The dosage is identical to the recommended daily dose above. Intravenous injection will be over several minutes; the administration of the infusion at the recommended daily dose will be done continuously over a period of 24 hours.

4.3. Contraindications

Hypersensitivity to piracetam or pyrrolidone derivatives or to any of the excipients listed in section 6.1
Piracetam is contraindicated in patients with cerebral hemorrhage and in patients with end stage renal disease, as well as patients with Huntington’s Chorea.

4.4. Special warnings and precautions for use

Effects on platelet aggregation
Due to the effect of piracetam on platelet aggregation (see section “5.1. Pharmacodynamic properties”), caution is necessary when using it in patients with severe bleeding, in patients with bleeding risk such as gastrointestinal ulcers, in patients with underlying haemostasis problems, patients with a history of hemorrhagic stroke, patients who need to have major surgery, including dental surgery and patients who take anticoagulants or antiplatelet agents, including low-dose aspirin.

Renal insufficiency
Piracetam is eliminated renally and caution is necessary in cases of renal insufficiency (see section 4.2).

Elderly
During long term treatment in the elderly, creatinine clearance should be regularly checked in order to adjust the dosage if necessary (see section 4.2)
Treatment discontinuation

Sudden treatment discontinuation should be avoided in myoclonic patients because the risk of myoclonus or generalized seizures is increased.

Precautions relative to excipients

- Mannitol (E421), contained in Nootropil 2400 mg granules for oral solution, may have a slight laxative effect when the daily dose of piracetam is 6.5 g or more.

- Nootropil 2400 mg granules for oral solution contain aspartame (E951), a source of phenylalanine, equivalent to 50 mg for a dose of 2.4 g of piracetam. Granules for oral solution are contraindicated in people with phenylketonuria.

- Glycerol contained in oral Nootropil solutions may induce headaches, upset stomach and diarrhoea.

- The presence of methyl paraben and propyl paraben in Nootropil oral solutions may cause allergic reactions (possibly delayed).

- Sodium:
  - Nootropil 800 mg and 1200 mg film-coated tablets contain approximately 2 mmol (or approximately 46 mg) of sodium per 24 g of piracetam.
  - Nootropil 20% oral solution contains approximately 3.5 mmol (or approximately 80.5 mg) of sodium per 24 g of piracetam.
  - Nootropil 33% oral solution contains approximately 1 mmol (or approximately 23 mg) of sodium per 24 g of piracetam.
  - Nootropil 1 g/5 ml and 3 g/15 ml solution for injection contains approximately 1 mmol (23 mg) of sodium per 24 g of piracetam.
  - Nootropil 12 g/60 ml solution for infusion contains approximately 19 mmol (or approximately 445 mg) of sodium per 24 g of piracetam.

To be considered in patients controlling their dietary sodium intake.

4.5. Interaction with other medicinal products and other forms of interaction

Thyroid hormones

Confusion, irritability and sleep disorders have been reported when taking Nootropil and thyroid extract (T3 + T4) concomitantly.

Acenocoumarol

In one published single-blind clinical study in patients with severe recurrent venous thrombosis, piracetam at a dose of 9.6 g/day did not change the doses of acenocoumarol necessary to reach INR 2.5 to 3.5, but compared to the effects of acenocoumarol alone, the addition of piracetam 9.6 g/day significantly reduced platelet aggregation, the release of β-thromboglobulin, fibrinogen and von Willebrand factors (VU: C; VIII: vW: Ag; VIII: vW: Rco) and total blood and plasma viscosity.

Pharmacokinetic interactions

The potential drug interactions resulting in changes in piracetam pharmacokinetics are expected to be low, since approximately 90% of the piracetam dose is excreted in the unchanged form in the urine.

In vitro, piracetam does not inhibit the main isoforms of human hepatic cytochrome P450 (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9/11) at concentrations of 142, 426 and 1422 µg/ml.
At 1422 µg/ml, minor inhibitor effects are observed on CYP 2A6 (21%) and 3A4/5 (11%). However, the Ki values for inhibition of these two CYP isoforms are likely to be far beyond 1422 µg/ml. Consequently, metabolic interactions of piracetam with other medicinal products are not very likely.

**Antiepileptic medicinal products**

A daily dose of 20 g piracetam for 4 weeks did not change the high and low levels of antiepileptics (carbamazepine, phenytoin, phenobarbital, and valproate) in epileptic patients receiving stable doses.

**Alcohol**

The concomitant administration of alcohol does not have any effect on plasma levels of piracetam and alcohol levels are not changed by 1.6 g of oral piracetam.

**4.6 Fertility, pregnancy and breast-feeding**

**Pregnancy**

Animal studies have not shown direct or indirect detrimental effects on gestation, embryonic or foetal development, childbirth and post-natal development (see section 5.3). There are insufficient relevant data on the use of piracetam in pregnant women. Piracetam crosses the placental barrier. In neonates, the level of the medicine is approximately 70 to 90% of the mother. Piracetam should not be used unless absolutely necessary, if the benefit exceeds the risk and the clinical conditions of the pregnant woman justify piracetam-based treatment.

**Breast-feeding**

Piracetam is excreted in breast milk. Accordingly, piracetam should not be used when breast-feeding or breast-feeding should be interrupted during piracetam treatment. It must be decided whether to interrupt breast-feeding or to interrupt piracetam treatment, depending on the benefit of breast-feeding for the child relative to the benefit of the treatment for the woman.

**4.7. Effects on ability to drive and use machines**

Due to the adverse reactions observed with this medicinal product, an influence on the ability to drive and use machines is possible and should be taken into consideration.

**4.8. Undesirable effects**

**a. Summary of the safety profile**

Placebo-controlled double-blind clinical or pharmacokinetic studies, from which quantified safety data have been extracted (extracts from the UCB data bank in June 1997), include more than 3000 subjects who received piracetam, without taking into account the indication, dosage, daily dosage regimen or the population characteristics.

**b. Tabulated list of adverse reactions**

The adverse reactions reported during clinical studies and after marketing of the product are given below by organ system and frequency. Frequency is defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, <1/1 000), very rare (<1/10 000) frequency undetermined (cannot be estimated on the basis of the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

**Haematological and lymphatic system disorders:**

Frequency undetermined: bleeding disorders.
**Immune system disorders:**
Frequency undetermined: anaphylactic reactions, hypersensitivity

**Psychiatric disorders:**
Common: nervousness
Uncommon: depression
Frequency undetermined: agitation, anxiety, confusion, hallucinations

**Nervous system disorders:**
Common: hyperactivity
Uncommon: drowsiness
Frequency undetermined: ataxia, impaired balance, worsening of pre-existing epilepsy, headache, insomnia, tremors

**Ear and labyrinth disorders:**
Frequency undetermined: vertigo

**Vascular disorders:**
Rare: thrombophlebitis (only for the injectable form), hypotension (only for the injectable form)

**Gastrointestinal disorders:**
Frequency undetermined: abdominal pain, upper abdominal pain, diarrhoea, nausea, vomiting

**Skin and subcutaneous tissue disorder:**
Frequency undetermined: angioedema, dermatitis, pruritus, urticaria

**Reproductive system and breast disorders:**
Frequency undetermined: sexual stimulation

**General disorders and administration site abnormalities:**
Uncommon: asthenia
Rare: pain at the injection site (only for the injectable form), pyrexia (only for the injectable form)

**Investigations:**
Common: weight gain

4.9. Overdose

**Symptoms of overdose**
No additional adverse reaction has been reported after an overdose.

The strongest overdose reported with piracetam was an oral dose of 75 g of piracetam. Bloody diarrhoea with abdominal pain was probably related to the extremely high dose of sorbitol contained in the formulation used.

**Treatment of overdose**
During a significant acute overdose the stomach may be emptied by gastric lavage or induced vomiting. There is no specific antidote. Overdose treatment will be symptomatic and may include hemodialysis. The efficacy of dialyzer extraction is from 50 to 60% for piracetam.

Certified translation by Christophe Vercruysse, certified translator at the Court of First Instance of Kortrijk, on 11 February 2015
5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: nootrope, ATC Code: N06B X03

Piracetam is a nootropic agent, i.e., a psychotropic medicinal product that directly ameliorates the efficacy of telencephalic functions.

Piracetam exerts its actions on the central nervous system by different pathways: modulation of brain neurotransmission, amelioration of metabolic conditions for neuronal plasticity, and improvement of microcirculation by its haemorheological properties, without vasodilation.

Chronic or acute administration of piracetam in patients with impaired brain function appears to induce significant EEG changes, indicating increased alertness and cognitive functioning (increased alpha and beta activity and decreased delta activity).

Piracetam protects and restores cognitive capacities after various types of brain insults, such as hypoxia, poisoning and electroshock treatment.

Piracetam is indicated alone or in combination in the treatment of cortical myoclonus. Piracetam reduces the duration of induced vestibular nystagmus.

Piracetam inhibits activated platelet hyperaggregability. In cases of abnormal rigidity, piracetam increases the filterability and deformability of red blood cells.

5.2. Pharmacokinetic properties

After oral administration (in tablets or oral solution), piracetam is quickly and almost completely resorbed by the gastrointestinal tract. Bioavailability is close to 100%.

A single dose of 2 g gives a maximum blood concentration of 40 to 60 µg/ml after 30 minutes, a concentration that appears in the cerebrospinal fluid between 2 and 8 hours.

The apparent distribution volume is around 0.6 l/kg.

The half-life is 4 to 5 hours in the blood and 6 to 8 hours in the cerebrospinal fluid. The half-life is prolonged in cases of renal insufficiency.

Piracetam is not bound to plasma proteins and is eliminated as is, mainly renally. Urinary elimination is practically complete (more than 95%) after 30 hours. Renal clearance of piracetam in healthy volunteers is 86 ml/minute.

Piracetam diffuses in all tissues and crosses the blood-brain and placental barriers, as well as the membranes used for renal dialysis.

Piracetam is active as is, it is not metabolized in any animal species.

Piracetam is concentrated in the cerebral cortex (frontal, parietal and occipital lobes), the cerebellar cortex and the basal ganglia.
5.3. Preclinical safety data
Data not provided

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Nootropil 800 mg film-coated tablets
Core: Macrogol 6000 - Colloidal anhydrous silica - Magnesium stearate - Croscarmellose sodium.
Coating: Hydroxypropylmethylcellulose - Titanium dioxide (EL71) - Macrogol 400 - Macrogol 6000.

Nootropil 1200 mg film-coated tablets:
Core: Macrogol 6000 - Colloidal anhydrous silica - Magnesium stearate - Croscarmellose sodium.
Coating: Hydroxypropylmethylcellulose - Titanium dioxide (E171) - Macrogol 400 - Macrogol 6000.

Nootropil 2400 mg granules for oral solution:
Aspartame - anhydrous citric acid - Orange flavour - Lemon flavour - Mannitol.

Nootropil 20 % oral solution:
Glycerol (85%) - sodium acetate - sodium saccharin - methylparaben - propylparaben - apricot flavour - caramel flavour - acetic acid - purified water.

Nootropil 33 % oral solution:
Glycerol (85%) - sodium acetate - methylparaben - propylparaben - apricot flavour - caramel flavour - acetic acid - purified water.

Nootropil 1 g/5 ml solution for injection:
Sodium acetate - acetic acid - water for injection.

Nootropil 3 g/15 ml solution for injection:
Sodium acetate - acetic acid - water for injection.

Nootropil 12 g/60 ml solution for infusion:
Sodium acetate - sodium chloride - acetic acid - water for injection.

6.2. Incompatibilities
Not applicable.

6.3. Shelf life

Nootropil 800 mg film-coated tablets 4 years
Nootropil 1200 mg film-coated tablets: 4 years
Nootropil 2400 mg granules for oral solution: 3 years
Nootropil 20 % oral solution: 3 years
Nootropil 33 % oral solution: 5 years
Nootropil 1 g/5 ml solution for injection: 5 years
Nootropil 3 g/15 ml solution for injection: 5 years
Nootropil 12 g/60 ml solution for infusion: 5 years

Expiry: Refer to the date appearing on the package after EXP (month/year). The expiry date is the last day of the month given.

Certified translation by Christophe Vercruysse, certified translator at the Court of First Instance of Kortrijk, on 11 February 2015.
6.4 Special precautions for storage
Nootropil 2400 mg granules for oral solution:
Store at a temperature below 30°C.

For the other forms:
This medicinal product does not require any special storage precautions.

6.5. Nature and contents of container

Nootropil 800 mg film-coated tablets: boxes of 60, 90 and 120 tablets. PVC/aluminum trays.
Nootropil 1200 mg film-coated tablets: boxes of 40, 60 and 100 tablets. PVC/aluminum trays.
Nootropil 2400 mg granules for oral solution: boxes of 30 and 60 single dose pouches of paper /
aluminum / polyethylene / Surlyn® (ionomer resin).
Nootropil 20 % oral solution: amber glass bottles of 125 and 150 ml.
Nootropil 33 % oral solution: amber glass bottles of 125 ml.
Nootropil 1 g / 5 ml solution for injection: boxes of 12 and 60 colorless type I glass vials.
Nootropil 3 g / 15 ml solution for injection: boxes of 4, 12 and 30 colorless type I glass vials.
Nootropil 12 g / 60 ml solution for infusion: boxes of 1 and 5 colorless glass type II vials.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORITY HOLDER

UCB Pharma SA
Allee de la Recherche, 60
B-1070 Brussels

8. MARKETING AUTHORITY NUMBER(S)

Nootropil 800 mg film-coated tablets BE097291
Nootropil 1200 mg film-coated tablets: BE141592
Nootropil 2400 mg granules for oral solution: BE156895
Nootropil 20 % oral solution: BE242392
Nootropil 33 % oral solution: BE249925
Nootropil 1 g / 5 ml solution for injection: BE047503
Nootropil 3 g / 15 ml solution for injection: BE097282
Nootropil 12 g / 60 ml solution for infusion: BE141583

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

Date of the first authorisation:
Nootropil 800 mg film-coated tablets 21/11/1975
Nootropil 1200 mg film-coated tablets: 17/05/1988
Nootropil 2400 mg granules for oral solution: 14/01/1992
Nootropil 20 % oral solution: 15/01/1976
Nootropil 33 % oral solution: 17/05/1988

IA29 June 2009 + Type IB variation: new CSP/CCDS C2010-012 + Radiations 2010 + Storage conditions and shelf life + CSP 2013
November 2013

Certified translation by Christophe Vercruysse, certified translator at the Court of First Instance of Kortrijk,
on 11 February 2015
Nootropil 1 g/5 ml solution for injection: 14/04/1972
Nootropil 3 g/15 ml solution for injection: 21/11/1975
Nootropil 12 g/60 ml solution for infusion: 17/05/1988

Date of the latest renewal: unlimited validity

10. DATE OF REVISION OF THE TEXT

A. Latest date of revision of the summary of product characteristics: 11/2013
B. Date of approval of the summary of product characteristics: 01/2014

Certified translation by Christophe Vercruysse, certified translator at the Court of First Instance of Kortrijk, on 11 February 2015