Version 4, 02/2016

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nootropil 800 mg film-coated tablets
Nootropil 1200 mg film-coated tablets
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 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

Excipient(s) with known effect:
Nootropil 800 mg film-coated tablets contain 1.5 mg natrium per tablet
Nootropil 1200 mg film-coated tablets contain 2.3 mg natrium per tablet
Nootropil 20% oral solution contain 0.7 mg natrium per ml
Nootropil 33% oral solution contain natrium
Nootropil 1 g/5 ml and 3 g/15ml solution for injection contain natrium
Nootropil 12 g/60 ml solution for infusion contain 3.7 mg natrium per tablet

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, with a score line and overprinted N/N
Nootropil 1200 mg film-coated tablets:
White film-coated tablets, oblong, with a score line and overprinted N/N

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 score line is only to facilitate breaking for ease of swallowing and not to divide into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Nootropil is offered for the symptomatic improvement of memory or intellectual impairment in a pathological context, where dementia has not been diagnosed.

- Nootropil can reduce cortical myoclonus in certain patients. To test sensitivity to piracetam, a trial treatment can be undertaken for a limited period.

4.2 Posology and method of administration

Posology

Symptomatic treatment of memory and/or intellectual disorders
The recommended daily dose ranges from 2.4 g up to 4.8 g , in two or three sub-doses.

Treatment of cortical myoclonus
The daily dosage should begin at 7.2 g, increasing by 4.8 g every three or four days up to a maximum of 24 g, divided in two or three doses. Treatment with other anti-myoclonic medicinal products should be maintained at the same dosage. Depending on the clinical benefit obtained, the dosage of other such medicinal products should be reduced, if possible.

Once started, treatment with piracetam should be continued for as long as the original cerebral disease persists. In patients with an acute episode, spontaneous evolution may occur over time and an attempt should be made every 6 months to decrease or discontinue the medicinal treatment. This should be done by reducing the dose of piracetam by 1.2 g every two days (every three or four days in the case of a Lance and Adams syndrome, in order to prevent the possibility of sudden relapse or withdrawal seizures).

Special populations

Elderly
Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below). For long term treatment, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

Patients with renal impairment
As Nootropil is almost entirely eliminated via the kidneys, precautions must be taken when treating patients with renal failure, and for whom it is advisable to monitor renal function.

The increase in half-life is directly related to the deterioration of renal function and creatinine clearance. This also applies to elderly patients, in whom the excretion of creatinine depends on age.

The interval between intakes must be adjusted based on the renal function. Refer to the following table and adjust the dose as indicated.

To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CL_{cr} in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140\text{-}age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dl)} \quad (\times 0.85\ for\ women)$$

Renal Function	Creatinine clearance (ml/min)	Posology and frequency
Normal	> 80	usual daily dose, divided in 2 to 4 doses
Mild	50-79	2/3 usual daily dose, divided in 2 or 3 doses
Moderate	30-49	1/3 usual daily dose, divided in 2 doses
Severe	< 30	1/6 usual daily dose, 1 single intake
End-stage renal disease	-	contraindicated

Patients with hepatic impairment
No dose adjustment is needed in patients with solely hepatic impairment.
In patients with hepatic and renal impairment, adjustment of the dose is recommended (see "Patients with renal impairment" above).

Method of administration

The oral forms of Nootropil can be taken with or without food.
The film-coated tablets should be swallowed with a little liquid.

The injectable form should be used when oral administration is not possible. The posology is the same as the recommended daily dose above.
The solution for injection will be administered intravenously over several minutes.
The solution for infusion will be administered continuously at the recommended daily dose over a 24 hour period.

4.3 Contraindications

Hypersensitivity to piracetam or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.
Piracetam is contraindicated in patients with cerebral haemorrhage and 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), caution is recommended in patients with severe haemorrhage, patients at risk of bleeding such as gastrointestinal ulcers, in patients with underlying haemostasis, in patients with a history of haemorrhagic cerebro-vascular accident (CVA), in patients undergoing major surgery, including dental surgery and in patients taking anticoagulants or platelet antiaggregant drugs, including low dose acetylsalicylic acid.

Renal impairment
Piracetam is eliminated via the kidneys and care should be taken in cases of renal impairment (see section 4.2).

Elderly
For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed (see section 4.2).

Discontinuation
Abrupt discontinuation of treatment should be avoided in myoclonic patients, as there is a high risk of generalised myoclonus events or convulsions.

Warnings related to the excipients

- The glycerol contained in Nootropil oral solutions may cause headache, stomach upset and diarrhoea.

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

- Sodium:
  Nootropil 800 mg film-coated tablets contain 1.5mg sodium per tablet, equivalent to 0,08% of the WHO recommended maximum daily intake of 2 g sodium for an adult
  Nootropil 1200 mg film-coated tablets contain 2.3 mg sodium per tablet, equivalent to 0,12% of the WHO recommended maximum daily intake of 2 g sodium for an adult
  Nootropil 20% oral solution contain contain 0.7 mg sodium per ml, equivalent to 0,03% of the WHO recommended maximum daily intake of 2 g sodium for
  Nootropil 33% oral solution contain less than 1 mmol (23 mg) sodium per ml, that is to say essentially 'sodiumfree'.
  Nootropil 1 g/5 ml and 3 g/15 ml solution for injection less than 1 mmol (23 mg) sodium per ml, that is to say essentially 'sodiumfree'.
  Nootropil 12 g/60 ml solution for infusion contain 3.7 mg sodium per tablet, equivalent to 18.54% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

  To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

In vitro, piracetam does not inhibit the principal human liver cytochrome P450 isoforms (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 inhibitory effects on CYP 2A6 (21%) and 3A4/5 (11%) were observed. However, the Ki values for the inhibition of these two CYP isoforms are likely to be well in excess of 1422 µg/ml. Therefore, metabolic interactions of piracetam with other medicinal products are unlikely.

Thyroid hormones
Confusion, irritability and sleep disorders have been reported during concomitant treatment of Nootropil and thyroid extracts (T3 + T4).

Acenocoumarol
In a published single-blind study on patients with severe recurrent venous thrombosis, piracetam at a dose of 9.6 g/day did not modify the doses of acenocoumarol necessary to reach an INR of 2.5 to 3.5, but compared to the effects of acenocoumarol alone, the addition of piracetam 9.6 g/day significantly decreased platelet aggregation, β-thromboglobulin release, levels of fibrinogen and von Willebrand's factors (VIII: C; VIII: vW: Ag; VIII: vW: Rco) and whole blood and plasma viscosity.

Anti-epileptic drugs

A daily dose of 20 g of piracetam over 4 weeks did not alter the peak and trough levels of anti-epileptic drugs (carbamazepine, phenytoin, phenobarbital and sodium valproate) in patients with epilepsy receiving stable doses.

Alcohol
Concomitant administration of alcohol has no effect on plasma levels of piracetam, and alcohol levels are not altered by 1.6 g of piracetam by oral route.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal or foetal development, parturition and post-natal development (see section 5.3). There are no adequate data from the use of piracetam in pregnant women. Piracetam crosses the placental barrier. Drug levels in the newborn are approximately 70% to 90% of maternal levels.
Piracetam should not be used during pregnancy except in cases of absolute necessity, when the benefit exceeds the risks and the clinical condition of the pregnant mother requires treatment with piracetam.

Breastfeeding
Piracetam is excreted in human breast milk. Therefore, piracetam should not be used during breastfeeding or breastfeeding should be discontinued, while receiving treatment with piracetam. A decision must be made whether to discontinue breast-feeding or to discontinue piracetam therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Double-blind, placebo-controlled clinical or pharmacoclinical trials of which quantified safety data are available (extracted from the UCB Documentation Data Bank in June 1997) included over 3,000 subjects receiving piracetam, regardless of indication, dosage, daily dosage or population characteristics.

Tabulated summary of adverse reactions
The adverse reactions reported in clinical trials and from post-marketing experience are listed below by System Organ Class and frequency. The frequencies are defined as follows: 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 (cannot be estimated from the available data).
Post-marketing data are not adequate to support an estimation of occurrence in the population to be treated.

Blood and lymphatic system disorders
Not known: haemorrhagic disorders

Immune system disorders
Not known: anaphylactic responses, hypersensitivity

Psychiatric disorders
Common: nervousness
Uncommon: depression
Not known: agitation, anxiety, confusion, hallucination

Nervous system disorders
Common: hyperactivity
Uncommon: drowsiness
Not known: ataxia, balance impaired, aggravation of pre-existing epilepsy, headache, insomnia, tremor.

Ear and labyrinth disorders
Not known: vertigo

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

Gastrointestinal disorders
Not known: abdominal pain, abdominal pain upper, diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders
Not known: angioneurotic oedema, dermatitis, pruritus, urticaria

Reproductive system and breast disorders
Not known: sexual stimulation

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

Investigations
Common: weight increased

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
The highest reported overdose with piracetam was an oral intake of 75 g piracetam. The reported case of bloody diarrhoea with abdominal pain was probably related to the extreme high dose of sorbitol contained in the used formulation. No additional adverse reaction has been reported following an overdose.

Management
In the event of a significant, acute overdosage, the stomach may be emptied by gastric lavage or by inducing vomiting. There is no specific antidote. Treatment of an overdose will be symptomatic and may include haemodialysis. Dialysis extraction efficiency is 50% to 60% for piracetam.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nootropics, ATC code: N06B X03

Piracetam is a nootropic agent, i.e. a pyschotropic drug which directly improves the efficiency of telencephalic functions.

Piracetam exerts its effects on the central nervous system in various ways: modifying neurotransmission in the brain, improving metabolic conditions for neuronal plasticity and improving the microcirculation by means of its haemorrheological properties, without causing vasodilatation.

Chronic or acute administration of piracetam to patients presenting cerebral dysfunction appears to induce significant changes on the electroencephalogram showing increased vigilance and cognitive function (increased α and β activity and reduced δ activity).

Piracetam protects and restores cognitive capacities after various cerebral insults such as hypoxia, intoxications and electroconvulsive therapy.

Piracetam is indicated as a stand-alone treatment or in association for the treatment of cortical myoclonus. Piracetam reduces the duration of the vestibular neuronitis which is provoked.

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

5.2 Pharmacokinetic properties

Absorption
After oral administration (as tablets or oral solution), piracetam is quickly and almost completely reabsorbed by the gastro-intestinal tract. Its bioavailability is almost 100%. A single dose of 2 g gives a maximum plasma concentration of 40 to 60 µg/ml after 30 minutes, this concentration appears in the cerebrospinal fluid between 2 and 8 hours.

Distribution
Piracetam is not bound to plasma proteins and its apparent volume of distribution is approximately 0.6 l/kg. Piracetam is distributed in all tissues and crosses the blood-brain and placental barriers, as well as the membranes used during renal dialysis. Piracetam concentrates in the cerebral cortex (frontal, parietal and occipital lobes), the cerebral cortex and basal ganglia.

Biotransformation
Piracetam is active as it is and is not metabolised in any animal species.

Elimination
Its half-life is 4 to 5 hours in the blood and 6 to 8 hours in the cerebrospinal fluid. The half-life is extended in cases of renal failure. Piracetam is eliminated as is via the kidneys. Urinary elimination is virtually complete (over 95%) after 30 hours.
Renal clearance of piracetam in healthy volunteers is 86 ml/minute.

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 (E171) – 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 20% oral solution
Glycerol (85%) – Sodium acetate – Sodium saccharin – Methyl parahydroxybenzoate – Propyl parahydroxybenzoate – Apricot flavour – Caramel flavour – Glacial acetic acid – Purified water.

Nootropil 33% oral solution
Glycerol (85%) – Sodium acetate – Methyl parahydroxybenzoate – Propyl parahydroxybenzoate – Glacial acetic acid – Purified water.

Nootropil 1 g/5 ml solution for injection
Sodium acetate – Glacial acetic acid – Water for injection.

Nootropil 3 g/15 ml solution for injection
Sodium acetate – Glacial acetic acid – Water for injection.

Nootropil 12 g/60 ml solution for infusion
Sodium acetate – Sodium chloride – Glacial 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 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

Expiration: Refer to date which is stated on the packaging after “EXP” (month/year). The expiry date refers to the last day of that month.

6.4 Special precautions for storage

These medicinal products do not require any special storage conditions.

6.5 Nature and contents of container

Nootropil 800 mg film-coated tablets: boxes of 60, 90 and 120 tablets. PVC - Aluminium blister.
Nootropil 1200 mg film-coated tablets: boxes of 40, 60 and 100 tablets. PVC - Aluminium blister.
Nootropil 20% oral solution: brown glass bottles containing 125 ml and 150 ml.
Nootropil 33% oral solution: brown glass bottles containing 125 ml.
Nootropil 1 g/5 ml solution for injection: boxes of 12 and 60 clear type I glass phials.
Nootropil 3 g/15 ml solution for injection: boxes of 4, 12 and 30 clear type I glass phials.
Nootropil 12 g/60 ml solution for infusion: boxes of 1 and 5 colourless glass vials closed by a rubber closure made of chlorobutyl elastomer.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60,
1070 Brussels

8. MARKETING AUTHORISATION NUMBERS

Nootropil 800 mg film-coated tablets: BE097291
Nootropil 1200 mg film-coated tablets: BE141592
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 AUTHORISATION

Date of first authorisation:
Nootropil 800 mg film-coated tablets: 21 January 1975
Nootropil 1200 mg film-coated tablets: 17 May 1988
Nootropil 20% oral solution: 15 January 1976
Nootropil 33% oral solution: 17 May 1988
Nootropil 1 g/5 ml solution for injection: 14 April 1972
Nootropil 3 g/15 ml solution for injection: 21 November 1975
Nootropil 12 g/60 ml solution for infusion: 17 May 1988

Date of latest renewal: 20 June 2008

10. DATE OF REVISION OF THE TEXT

Approval date of the text: 03/2020