Piracetam
Nootropil®
Solution for Injection

PRODUCT DESCRIPTION
Piracetam (Nootropil®) 1g/5mL: Each 5 mL injectable ampoule contains 1 g of piracetam
Piracetam (Nootropil®) 3g/15mL: Each 15 mL injectable ampoule contains 3 g of piracetam
Piracetam (Nootropil®) 12g/60mL Each 60 mL infusion contains 12 g of piracetam

PHARMACOLOGIC PROPERTIES
The active substance, piracetam, is a pyrrolidone (2-oxo-1-pyrrolidine-acetamide), a cyclic derivative of gammaaminobutyric acid (GABA).

Mechanism of action
Available data suggest that piracetam's basic mechanism of action is neither cell nor organ specific. Piracetam (Nootropil®) binds physically in a dose-dependent manner to the polar head of phospholipid membrane models, inducing the restoration of the membrane lamellar structure characterised by the formation of mobile drug phospholipid complexes. This probably accounts for an improved membrane stability, allowing the membrane and transmembrane proteins to maintain or recover the three-dimensional structure or folding essential to exert their function. Piracetam has neuronal and vascular effects.

Neuronal effect
At the neuronal level, piracetam exerts its membrane activity in various ways. In animals, piracetam enhances a variety of types of neurotransmission, primarily through postsynaptic modulation of receptor density and activity. In both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness were enhanced, in the normal subject as well as in deficiency states, without the development of sedative or psychostimulant effects. Piracetam protects and restores cognitive abilities in animals and man after various cerebral insults such as hypoxia, intoxications and electroconvulsive therapy. It protects against hypoxia-induced changes in brain function and performance as assessed by electroencephalograph (EEG) and psychometric evaluations.

Vascular effects
Piracetam exerts its haemorrhological effects on the platelets, red blood cells, and vessel walls by increasing erythrocyte deformability and by decreasing platelet aggregation, erythrocyte adhesion to vessel walls and capillary vasospasm.

Effects on the red blood cells: In patients with sickle cell anaemia, piracetam improves the deformability of the erythrocyte membrane, decreases blood viscosity, and prevents rouleaux formation.

Effects on platelets: In open studies in healthy volunteers and in patients with Raynaud's phenomenon, increasing doses of piracetam up to 12 g was associated with a dose-dependent reduction in platelet functions compared with pre-treatment values (tests of aggregation induced by ADP, collagen, epinephrine and βTG release), without significant change in platelet count. In these studies, piracetam prolonged bleeding time.

Effects on blood vessels: In animal studies, piracetam inhibited vasospasm and counteracted the effects of various spasmodogenic agents. It lacked any vasodilatory action and did not induce "steal" phenomenon, nor low or no reflow, nor hypotensive effects. In healthy volunteers, piracetam reduced the adhesion of RBCs to vascular endothelium and possessed also a direct stimulant effect on prostacycline synthesis in healthy endothelium.

Effects on coagulation factors: In healthy volunteers, compared with pre-treatment values, piracetam up to 9.6 g reduced plasma levels of fibrinogen and von Willebrand's factors (VIII : C; VIII R : AG; VIII R : vW) by 30 to 40 %, and increased bleeding time. In patients with both primary and secondary Raynaud phenomenon, compared with pretreatment values, piracetam 8 g/d during 6 months reduced plasma levels of fibrinogen and von Willebrand's factors (VIII : C; VIII R : AG; VIII R : vW (RCF)) by 30 to 40 %, reduced plasma viscosity, and increased bleeding time. Another study in healthy volunteers did not show any statistically significant difference between piracetam (up to 12 g b.i.d.) and placebo regarding effects on haemostasis parameters and bleeding time.

Pharmacokinetics
The pharmacokinetic profile of piracetam is linear and time-independent with low intersubject variability over a large range of doses. This is consistent with the high permeability, high solubility, and minimal metabolism of piracetam. Plasma half-life of piracetam is 5 hours. It is similar in adult volunteers and in patients. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. Steady state plasma concentrations are achieved within 3 days of dosing.

Absorption
Piracetam is rapidly and extensively absorbed following oral administration. In fasted subjects, the peak plasma concentrations are achieved 1 hour after dosing. The absolute bioavailability of piracetam oral formulations is close to 100 %. Food does not affect the extent of absorption of piracetam but it decreases Cmax by 17 % and increases tmax from 1 to 1.5 hours. Peak concentrations are typically 84 μg/mL and 115 μg/mL following a single oral dose of 3.2 g and repeat dose of 3.2 g t.i.d., respectively.

Distribution
Piracetam is not bound to plasma proteins and its volume of distribution is approximately 0.6 L/kg. Piracetam crosses the blood brain barrier as it has been measured in cerebrospinal fluid following intravenous administration. In cerebrospinal fluid, the tmax was achieved about 5 hours post-dose and the half-life was about 8.5 hours. In animals, piracetam highest concentrations in the brain were in the cerebral cortex (frontal, parietal and occipital lobes), in the cerebellar cortex and in the basal ganglia. Piracetam diffuses to all tissues except adipose tissues, crosses placental barrier, and penetrates the membranes of isolated red blood cells.

Biotransformation
Piracetam is not known to be metabolized in the human body. This lack of metabolism is supported by the lengthy plasma half-life in anuric patients and the high recovery of parent compound in urine.

Elimination
The plasma half-life of piracetam in adults is about 5 hours following either intravenous or oral administration. The apparent total body clearance is 80-90 mL/min. The major route of excretion is via urine, accounting for 80 to 100 % of the dose. Piracetam is excreted by glomerular filtration.

Linearity
The pharmacokinetics of piracetam are linear over the dose range of 0.8 to 12 g. Pharmacokinetic variables like half-life and clearance are not changed with respect to the dose and the duration of treatment.

Special Patient Populations:
- **Gender**
  In a bioequivalence study comparing formulations at a dose of 2.4 g, Cmax and AUC were approximately 30% higher in women (N=6) compared to men (N=6). However, clearances adjusted for body weight were comparable.

- **Race**
  Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons involving Caucasians and Asians, however, show that pharmacokinetics of piracetam were comparable between the two races. Because piracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

- **Elderly**
  In the elderly, the half-life of piracetam is increased and the increase is related to the decrease in renal function in this population (see Dosage and Administration).

- **Children**
  No formal pharmacokinetic study has been conducted in children.

- **Renal impairment**
  Piracetam clearance is correlated to creatinine clearance. It is therefore recommended to adjust the daily dose of piracetam based on creatinine clearance in patients with renal impairment (see Dosage and Administration). In anuric End Stage Renal Disease subjects, the half-life of piracetam is increased up to 59 hours. The fractional removal of piracetam was 50 to 60% during a typical 4-hour dialysis session.

- **Hepatic impairment**
  The influence of hepatic impairment on the pharmacokinetics of piracetam has not been evaluated. Because 80 to 100% of the dose is excreted in the urine as unchanged drug, hepatic impairment solely would not be expected to have a significant effect on piracetam elimination.

**Preclinical safety data**

The preclinical data indicate that piracetam has a low toxicity potential. Single dose studies showed no irreversible toxicity after oral doses of 10 g/kg in mice, rats and dogs. No target organ for toxicity was observed in repeated dose, chronic toxicity studies in mice (up to 4.8 g/kg/day) and in rats (up to 2.4 g/kg/day). Mild gastrointestinal effects (emesis, change in stool consistency, increased water consumption) were observed in dogs when piracetam was administered orally for one year at a dose increasing from 1 to 10 g/kg/day. Similarly, i.v. administration of up to 1 g/kg/day for 4-5 weeks in rats and dogs did not produce toxicity. In *vitro* and *in vivo* studies have shown no potential for genotoxicity and carcinogenicity.

**INDICATIONS**

In adults:
- Symptomatic treatment of the psycho-organic syndrome whose features, improved by treatment, are memory loss, attention disorders and lack of drive.
- Treatment of cortical myoclonus, alone or in combination.
- Treatment of vertigo and associated disorders of balance, with the exception of dizziness of vasomotor or psychic origin.

In children:
- Treatment of dyslexia, in combination with appropriate measures such as speech therapy.

**DOSAGE AND ADMINISTRATION**

When parenteral administration is needed (e.g. swallowing difficulties, unconsciousness) piracetam can be administered intravenously at the same recommended daily dose.

- 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.

Recommended daily doses are provided below by indication.

**Symptomatic treatment of psycho-organic syndromes**

The recommended daily dose ranges from 2.4 g to 4.8 g, in two or three sub-doses.

**Treatment of myoclonus of cortical origin**

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, in two or three sub-doses. Treatment with other anti-myo-clinonic 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).

**Treatment of vertigo**

The recommended daily dose ranges from 2.4 g to 4.8 g, in two or three sub-doses.

**Dosage adjustment in elderly**

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

**Dosage adjustment in patients with renal impairment**

The daily dose must be individualized according to 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 CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

\[
CL_{cr} \ (mL/min) = \frac{[140-\text{age (years)} \times \text{weight (kg)}]}{85} \times 0.85 \quad (\text{for women})
\]

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, in two or three sub-doses.

**Treatment of dyslexia in combination with speech therapy**

In children from 8 years old and adolescents, the recommended daily dose is about 3.2 g, in two or three sub-doses.

**Dosage adjustment in children**

No formal pharmacokinetic study has been conducted in children.
### Pharmacologic Properties

- **Psychiatric Disorders:**
  - Related to a statistically significantly higher occurrence under treatment with piracetam.
  - This includes indications, dosage forms, daily dosages, or population characteristics.

- **UCB Documentation Data Bank on June 1997:**
  - Included more than 3000 subjects receiving piracetam, regardless of characteristics.

#### Clinical Studies

**ADVERSE EFFECTS**

- **Pregnancy and Lactation:**
  - Should be avoided during breastfeeding or breastfeeding should be discontinued, while receiving treatment with piracetam.

- **Effects on Ability to Drive and Use Machines:**
  - An influence on driving and using machines is possible.

- **Drug Interactions:**
  - Metabolic interaction of piracetam with other drugs is unlikely.

- **Dosage Adjustment in Patients with Hepatic Impairment:**
  - No dose adjustment is needed in patients with solely hepatic impairment.

- **Contraindications:**
  - Hypersensitivity to piracetam or other pyrrolidone derivatives or any of the excipients.

- **Warnings and Precautions:**
  - Due to the platelet antiaggregant effect of piracetam (see Pharmacologic properties), caution is recommended in patients with severe haemorrhage, at risk of bleeding such as gastrointestinal ulcer, patients with underlying disorders of haemostasis, patients with history of haemorrhagic CVA, patients undergoing major surgery including dental surgery, and patients using anticoagulants or platelet antiaggregant drugs including low dose aspirin.

  - Piracetam (Nootropil®) is eliminated via the kidneys and should thus be taken in cases of renal insufficiency (see Dosage and Administration).

  - For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

  - Abrupt discontinuation of treatment should be avoided in myoclonic patients as this may induce sudden relapse or withdrawal seizures.

- **Dosage Adjustment in Patients with Renal Impairment:**
  - Patients with renal impairment and renal dysfunction.

- **Dosage Adjustment in Patients Undergoing Dialysis:**
  - Contraindicated.

#### Pharmacokinetics

- **Metabolism:**
  - Approximately 90% of the dose of piracetam is excreted in the urine as unchanged drug.

- **Renal Excretion:**
  - Patients with renal impairment or undergoing dialysis.

- **Drug Interactions:**
  - Piracetam may cause a decrease in the antiplatelet effect of aspirin, and a potential increase in bleeding in patients using anticoagulants or platelet antiaggregant drugs including low dose aspirin.

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• central and peripheral nervous system disorders
• metabolic and nutritional disorders
• body as a whole- general disorders.

The following adverse experiences were reported for piracetam with a statistically significantly higher incidence than placebo. Incidences are given for piracetam (n = 3017) versus placebo (n= 2850) treated patients.

<table>
<thead>
<tr>
<th>WHO System Organ Class</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
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<tr>
<td>Hyperkinesia</td>
<td>(1.72 vs. 0.42%)</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
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<tr>
<td>Weight increased</td>
<td>(1.29 vs. 0.39%)</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
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<tr>
<td>Nervousness</td>
<td>(1.13 vs 0.25%)</td>
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<tr>
<td>Somnolence</td>
<td>(0.96 vs 0.25%)</td>
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<tr>
<td>Depression</td>
<td>(0.83 vs 0.21%)</td>
<td></td>
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<tr>
<td>General disorders and administration</td>
<td></td>
<td></td>
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<tr>
<td>site conditions</td>
<td></td>
<td>Asthma</td>
</tr>
</tbody>
</table>

Post-marketing experience
From the post-marketing experience, the following additional adverse drug reactions have been reported (sorted according to MedDRA System Organ Classes). Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and Lymphatic disorders: haemorrhagic disorder
Ear and labyrinth disorders: vertigo
Gastrointestinal disorders: abdominal pain, abdominal pain upper, diarrhoea, nausea, vomiting
Immune system disorders: anaphylactoid reaction, hypersensitivity
Nervous system disorders: ataxia, balance impaired, epilepsy aggravated, headache, insomnia
Psychiatric disorders: agitation, anxiety, confusion, hallucination
Skin and subcutaneous tissue disorders: angioneurotic oedema, dermatitis, pruritus, urticaria

Rare cases of injection site pain, thrombophlebitis, pyrexia or hypotension have been reported after intravenous administration.

OVERDOSAGE AND TREATMENT
Symptoms
One case of bloody diarrhoea with abdominal pain, associated with the oral intake of 75 g piracetam daily, was most probably related to the extreme high dose of sorbitol contained in the used formulation.
No other case was reported that would point to additional adverse events specifically related to overdose.

Treatment
In acute, significant overdosage, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for overdose with piracetam. Treatment for an overdose will be symptomatic treatment and may include haemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.

STORAGE CONDITIONS
Piracetam (Nootropil®) 1g/5mL, 3g/15mL solution for injection: Store at temperatures not exceeding 25°C
Piracetam (Nootropil®) 12g/60mL solution for intravenous infusion: Store at temperatures not exceeding 30°C

AVAILABILITY
Piracetam (Nootropil®) 1g/5mL solution for injection: 5 mL ampoules (box of 12’s)
Piracetam (Nootropil®) 3g/15mL solution for injection: 15 mL ampoules (box of 4’s)
Piracetam (Nootropil®) 12g/60mL solution for intravenous infusion: glass bottle of 60 mL

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

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Pianezza (TO), Italy