

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NOOTROPIL Oral Solution 33% w/v.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Piracetam – 33% w/v (1ml contains 0.333g of Piracetam).

Excipients: contains 1.8 mg/ml methylparahydroxybenzoate and 0.2mg/ml propyl parahydroxybenzoate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Solution.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of cortical myoclonus, alone or in combination.

4.2 Posology and method of administration

Nootropil Oral Solution 33% w/w will be administered orally and may be taken with or without food.

Adults:

The daily dosage should begin at 7.2 g/day, increasing by 4.8 g/day every 3 days up to a maximum of 24 g/day, given in either 2 or 3 divided doses.

Treatment with other antimyoclonic drugs should remain unchanged at their optimal dosage. If possible, depending on clinical benefit, an attempt should be made to subsequently reduce the dosage of other antimyoclonic drugs.

Once started treatment should be continued for as long as the condition persists. In patients with an acute episode, spontaneous evolution may occur over time and an attempt should be made at six month intervals to decrease or discontinue treatment. This may be accomplished by gradually reducing the daily piracetam dose by 1.2 g at two day intervals (or four days in the case of Lance or Adams syndrome) so as to prevent the possibility of sudden relapse or withdrawal seizures.

Dosage adjustment in elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function (*refer to section 4.4, Special warnings and precautions for use*). 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 section 4.4, Special warnings and precautions for use*).

Dosage adjustment in patients with hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic and renal impairment, adjustment of dose is recommended (*refer to section 4.4, special warnings and precautions for use*).

4.3 Contraindications

Hypersensitivity to piracetam or other pyrrolidone derivatives or any of the excipients.
Piracetam is contra-indicated in patients with cerebral haemorrhage.
Piracetam is contra-indicated in End Stage Renal Disease patients.
Piracetam is contra-indicated in patients suffering from Huntington’s Chorea.

4.4 Special warnings and precautions for use

Due to the effect of piracetam on platelet aggregation (*see section 5.1 Pharmacodynamic properties*), caution is recommended in patients with underlying disorders of haemostasis, major surgery or severe haemorrhage.

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

As piracetam is almost exclusively excreted by the kidneys caution should be exercised in treating patients with known renal sufficiency. For long term treatment in elderly patients, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

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:

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

Group	Creatine clearance (ml/ dl)	Posology and frequency
Normal	> 80	Usual daily dose 2 to 4 sub-dose
Mild	50-79	2/3 usual daily dose, 2 or 3 sub-doses
Moderate	30-49	1/3 usual daily dose, 2 sub doses
Severe	< 30	1/6 usual daily dose, 1 single intake
End stage renal		contraindicated
Disease		

4.5 Interaction with other medicinal products and other forms of interaction

In a single case, confusion, irritability and sleep disorders were reported in concomitant use with thyroid extract (T3 + T4).

In a published single-blind study on patients with severe recurrent venous thrombosis, piracetam 9.6 g/d did not modify the doses of acenocoumarol necessary to reach INR 2.5 to 3.5, but compared with the effects of acenocoumarol alone, the addition of piracetam 9.6 g/d 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.

The drug interaction potential 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 human liver cytochrome P450 isoforms CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9/11 at concentrations of 142, 426 and 1422 ug/ml. At 1422 ug/ml, minor inhibitory effects on CYP 2A6 (21%) and 3A4/5 (11%) were observed. However, the K_i values for inhibition of these two CYP isoforms are likely to be well in excess of 1422 ug/ml. Therefore, metabolic interaction of piracetam with other drugs is unlikely. A 20 g daily of piracetam over 4 weeks did not modify the peak and trough serum levels of antiepileptic drugs (carbamazepine, phenytoin, phenobarbitone, valproate) in epileptic patients who were receiving stable doses.

Concomitant administration of alcohol had no effect on piracetam serum levels and alcohol levels were not modified by a 1.6 g oral of piracetam.

4.6 Pregnancy and lactation

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or post-natal development.

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 unless clearly necessary. Piracetam is excreted in human breast milk. Therefore, piracetam should be avoided during breastfeeding or breastfeeding should be discontinued, while receiving treatment with piracetam.

4.7 Effects on ability to drive and use machines

Given the adverse events observed with the drug, an influence on driving and using machines is possible and should be taken into account.

4.8 Undesirable effects

A. Clinical studies

Double-blind placebo-controlled clinical or pharmacoclinical trials, of which quantified safety data are available (extracted from the UCB Documentation Data Bank on June 1997), including more than 3000 subjects receiving piracetam, regardless of indication, dosage form, daily dosage or population characteristics.

When adverse events are grouped together according to WHO System Organ Classes, the following classes were found to be related to a statistically significantly higher occurrence under treatment with piracetam: psychiatric disorders, central and peripheral nervous system disorders, metabolic and nutritional disorders, body as a whole - general disorders.

Following adverse experiences were reported for piracetam with a statistically significantly higher incidence than placebo. Incidences are given for piracetam versus placebo treated patients.

WHO System Organ Class	Common (> 1%, ≤ 10%)	Uncommon (> 0.1%, ≤ 1%)
Central and peripheral nervous system disorders	Hyperkinesia (1.72 versus 0.42%)	
Metabolic and nutritional disorders	Weight increase (1.29 versus 0.39%)	
Psychiatric disorders	Nervousness (1.13 versus 0.25%)	Somnolence (0.96 versus 0.25%) Depression (0.83 versus 0.21%)
Body as a whole-general disorders		Asthenia (0.23 versus 0.00%)

B. Post-marketing experience

From the post-marketing experience, the following 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.

- *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, somnolence
- *Psychiatric disorders:*
agitation, anxiety, confusion, hallucination
- *Skin and subcutaneous tissue disorders:*
angioneurotic oedema, dermatitis, pruritus, urticaria, rash

4.9 Overdose

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.

Management of overdose

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 hemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nootropics,
ATC code: N06B X03.

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

Available data suggest that piracetam basic mechanism of action is neither cell-nor organ specific. Piracetam binds physically in a dose-dependent manner to the polar head of phospholipids membrane models, inducing the restoration of the membrane lamellar structure characterised by the formation of mobile drug-phospholipid complexes.

This probably accounts for 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.

At the neuronal levels, 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.

Piracetam exerts its haemorrheological 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 β TG 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 spasmogenic 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 pre-treatment values, piracetam of 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 hemostasis parameters and bleeding time.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of piracetam is linear and time-independent with low inter-subject 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 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 C_{max} by 17% and increases t_{max} 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 t_{max} 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 metabolised 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.

Characteristics in patients

Gender

In a bioequivalence study comparing formulations at a dose of 2.4 g, C_{max} and AUC were approximately 30% higher in women (N=6) compared to men (N=6). However, clearance 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 section 4.2, Posology and method of 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 section 4.2, Posology and method of 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.

5.3 Preclinical safety data

The preclinical data indicate that piracetam has a low toxicity potential. Single dose studies showed no irreversible toxicity after oral dose 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium acetate
Glacial acetic acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

A 300 ml amber glass bottle (type III, Ph. Eur.), closed with a polypropylene child proof cap with a polyethylene liner including a graduated (1-25 ml) polypropylene measuring device.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

UCB (Pharma) Ireland Limited
United Drug House
Belgard Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0891/001/001

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