NOOTROPIL®
Piracetam

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 mg or 1200 mg of piracetam.
Each ml of oral solution contains 200 mg of piracetam

EXCIPIENTS

NOOTROPIL 800 mg and 1200 mg film-coated tablet:
Core:
Macrogol 6000 - Colloidal anhydrous silica - Magnesium stearate - Sodium croscarmellose
Film-coating:
Hydroxypropylmethylcellulose - Titanium dioxide (E171) - Macrogol 400 - Macrogol 6000.

NOOTROPIL 200 mg/ml oral solution:
Glycerol (85%) - Saccharin sodium - Apricot flavour - Caramel flavour - Methyl parahydroxybenzoate - Propyl parahydroxybenzoate - Sodium acetate - Glacial acetic acid - Purified water.

PHARMACEUTICAL FORM

NOOTROPIL Tablet 800 and 1200 mg: white, oblong, film-coated tablet, with a bisect line, marked N/N on one side and plain on the other side
NOOTROPIL Oral Solution 20%: clear colourless solution

INDICATIONS

1. Studies carried out in the elderly suffering from loss of memory, vertigo, a lack of concentration or of alertness, changes of mood, a deterioration in behaviour and personal negligence, demonstrate an improvement in symptoms.
These symptoms can also provide an early warning of the onset of pathological ageing such as Alzheimer's Disease, an Alzheimer type of senile dementia, or the dementia produced by multiple cerebral infarcts.
2. NOOTROPIL is advocated in the treatment of sickle-cell vaso-occlusive crises.
3. Studies have shown some improvement in children with learning difficulties associated with the written word, particularly with textual understanding which cannot be explained by intellectual backwardness, inadequate education or by the family environment. The administration of NOOTROPIL does not replace other measures also well adapted to correct these learning difficulties, such as remedial teaching.

DOSAGE AND ADMINISTRATION

Oral formulations

NOOTROPIL should be administered orally, and may be taken with or without food. The film-coated tablets should be swallowed with liquid.

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

Route of Administration

Oral formulations

For oral use.

Parenteral formulations

For intravenous use.

The total daily dose can range from 30 to 160 mg/kg/day depending on the indication. This is administered twice daily, but may also be given in three or four separate doses.
– When treating severe symptoms, 12 g daily may need to be administered as an intravenous infusion.
– NOOTROPIL, as a long-term therapy for psycho-organic syndrome in the elderly is given in doses ranging from 1.2 to 2.4 g daily, according to the severity of the symptoms. The loading dose can be as high as 4.8 g/day during the initial weeks of treatment.
– When treating sickle-cell vaso-occlusive crises, the dose administered is 160 mg/kg/day divided in four equal doses.
– In the treatment of 8 to 13 year-old children with learning difficulties NOOTROPIL is given at a total dose of 3.3 g daily. This is administered either as 8 ml of a 20% solution twice a day i.e. before breakfast and before the evening meal.
The medication may be more easily accepted if given in fruit juice, or in some other drink. Treatment should be continued throughout the school year. The efficacy of a longer period of treatment has not yet been investigated.

Elderly
Adjustment of the dose is recommended in elderly patients with compromised renal function (*see Sections: Warnings and Precautions; Renal Impairment below*). For long term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

Renal impairment
Piracetam is contraindicated in severe renal impairment (renal creatinine clearance of less than 20 ml per minute) (*see Sections: Contraindications; Warnings and Precautions*). The daily dose must be individualised 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 (CL_{cr}) 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}= [140 – age (*years*)] X weight (*kg*) (X 0.85 for women)

72 X serum creatinine (*mg/dl*)

Group	Creatinine Clearance (ml/min)	Posology and frequency
Normal	> 80	usual daily dose, 2 to 4 divided doses
Mild	50-79	2/3 usual daily dose, 2 or 3 divided doses
Moderate	30-49	1/3 usual daily dose, 2 divided doses
Severe	20 - 29	1/6 usual daily dose, 1 single intake
	< 20	Contraindicated
End-stage renal disease	**--**	Contraindicated

Hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of dose is recommended (*see dose adjustment in Renal Impairment above).*

CONTRAINDICATIONS

NOOTROPIL is contraindicated in:

- Hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients;
- Patients with severe renal impairment (renal creatinine clearance of less than 20 ml per minute);
- Patients with cerebral haemorrhage;
- Patients suffering from Huntington's Chorea.

WARNINGS & PRECAUTIONS

Effects on platelet aggregation

Due to the effect of piracetam on platelet aggregation, caution is recommended in patients with severe haemorrhage, patients 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 acetylsalicylic acid.

Renal insufficiency

Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency (*see Section: Dosage and Administration*).

Elderly

For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed (*see Section: Dosage and Administration*).

Discontinuation

Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalised seizures in some myoclonic patients.

Sickle-cell vaso-occlusive crises

For sickle-cell indication, a dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Warnings related to the excipients:

NOOTROPIL 800 mg, film-coated tablet
NOOTROPIL 1200 mg, film-coated tablet
Sodium
These products contain about 2 mmol (or about 46 mg) sodium per 24 g piracetam. This should be taken into consideration by patients on a controlled sodium diet.

NOOTROPIL 200 mg/ml, oral solution
Sodium
This product contains about 3.5 mmol (or about 80.5 mg) sodium per 24 g piracetam. This should be taken into consideration by patients on a controlled sodium diet.

Methyl parahydroxybenzoate and propylparahydroxybenzoate
This medicinal product contains methyl parahydroxybenzoate and propylparahydroxybenzoate which may cause allergic reactions (possibly delayed) *(see Section: Adverse Reactions)*.

Glycerol
This medicinal product contains glycerol which may cause headache, stomach upset and diarrhoea *(see Section: Adverse Reactions)*.

INTERACTIONS

Pharmacokinetic interactions
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 µg/ml. At 1422 µg/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 µg/ml.

Therefore, metabolic interaction of piracetam with other drugs is unlikely.

Thyroid hormones
Confusion, irritability and sleep disorder have been reported during concomitant treatment with thyroid extract (T3 + T4).

Acenocoumarol
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.

Antiepileptic drugs
A 20 g daily dose 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.

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

PREGNANCY AND LACTATION

Fertility
There are no relevant data available.

Pregnancy
Piracetam should not be used during pregnancy unless clearly necessary, when benefit exceeds the risks and the clinical condition of the pregnant mother requires treatment with piracetam.

There are no adequate data from the use of piracetam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development.
Piracetam crosses the placental barrier. Drug levels in the newborn are approximately 70% to 90% of maternal levels.

Lactation
Piracetam should not be used during breast-feeding or breast-feeding 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.
Piracetam is excreted in human breast milk.

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

In view of the undesirable side effects, which were observed after the administration of the preparation, there is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.

UNDESIRABLE EFFECTS

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), included more than 3000 subjects receiving piracetam, regardless of indication, dosage form, daily dosage or population characteristics.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥1/10000 to <1/1000

Very rare <1/10000

Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Not known: haemorrhagic disorder

Immune system disorders

Not known: anaphylactoid reaction, hypersensitivity

Psychiatric disorders

Common: nervousness

Uncommon: depression

Not known: agitation, anxiety, confusion, hallucination

Nervous system disorders

Common: hyperkinesia

Uncommon: somnolence

Not known: ataxia, balance impaired, epilepsy aggravated, headache, insomnia

Ear and labyrinth disorders

Not known: vertigo

Vascular disorders

Rare: thrombophlebitis (only for injectable form), hypotension (only for 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

General disorders and administration site conditions

Uncommon: asthenia

Rare: pyrexia (only for injectable form), injection site pain (only for injectable form)

Investigations

Common: weight increased

OVERDOSAGE

Symptoms and signs

No additional adverse events specifically related to overdose have been reported with piracetam.

The highest reported overdose with piracetam was oral intake of 75 g wherein bloody diarrhoea with abdominal pain, was most probably related to the extreme high dose of sorbitol contained in the used formulation.

Treatment

There is no specific antidote for overdose with piracetam. Treatment for an overdose should be symptomatic and may include haemodialysis. The extraction efficiency of the dialyser is 50 to 60% for piracetam.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group

Psychostimulants, agents used for ADHD and nootropics.

ATC Code

N06BX03

Mechanism of Action

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 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.

Pharmacodynamic 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 applies its haemorrhagic effect to thrombocytes, erythrocytes and the walls of the blood vessels by increasing the deformability of erythrocytes, reducing the aggregability of thrombocytes, reduces the adhesion of erythrocytes to the walls of vessels and reduces 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’s 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.

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 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.

Metabolism
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.

Special patient populations

Children
No formal pharmacokinetic study has been conducted in children.

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 Dosage and Administration)*.

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: Dosage and Administration*).

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.

Other patient characteristics

Race
Formal pharmacokinetic studies of the effects of race have not been conducted. Because piracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies
see Section Pharmacodynamic effects

NON-CLINICAL INFORMATION

Single doses of piracetam yielded LD 50 values at 26 g/kg in mice but LD 50 values were not reached in rats. In dogs, clinical signs after acute oral dosing were mild and lethality was not observed at the maximum tested dose of 10 g/kg.

Repeated oral treatment for up to 1 year in dogs (10 g/kg) and 6 months in rats (2 g/kg) was very well tolerated: no target organ toxicity or signs of (irreversible) toxicity were clearly demonstrated. Safe dose levels represent a multiple of the maximum intended human daily dose of 0.4 g/kg.

In terms of exposure (C_{max}) safe levels obtained in the rat and the dog represent respectively 8 fold and 50 fold of the maximum human therapeutic level. AUC levels obtained in the same animals were a multiple of the human AUC level at the maximum intended daily dose.

The only change which might eventually be attributed to chronic treatment in male, but not in female, rats was an increase of the incidence over control animals of progressive glomerulonephrosis at the dose of 2.4 g/k/day given for 112 weeks.

Although piracetam crosses the placenta into the foetal circulation, no teratogenic effects were observed at dose levels up to 4.8 g/kg/day (mice, rats) and 2.7 g/kg/day (rabbits). Furthermore, the compound affects neither fertility nor the peri- or postnatal development of the pregnancy at doses up to 2.7 g/kg/day.

Piracetam was found to be devoid of any mutagenic or clastogenic activity and does not represent any genotoxic or carcinogenic risk to man.

PHARMACEUTICAL INFORMATION

Shelf-Life

As registered locally.

Storage

Refer to the storage condition on the outer packaging.

Nature and Contents of Container

Oral preparations:
– 90 Film-coated tablets of piracetam 800 mg
– 20 Film-coated tablets of piracetam 1200 mg
– 125 ml Bottle of 20% solution (1 ml = 200 mg piracetam)

Not all presentations will be available locally.

Incompatibilities

There are no known incompatibilities.

Use and Handling

There are no special requirements for use or handling of this product.

Manufacturer for oral solution: NEXTPHARMA SAS LIMAY, FRANCE.	Manufacturer for tablets: UCB PHARMA SA BRAINE-L'ALLEUD, BELGIUM.

Version number: NCDS03 SI

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