Nootropil

Piracetam

NAME OF THE MEDICINAL PRODUCT

Nootropil Tablet 800mg

Nootropil Tablet 1200mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Nootropil Tablet 800mg

Each film-coated tablet contains 800mg of piracetam.

Nootropil Tablet 1200mg

Each film-coated tablet contains 1200mg of piracetam.

Excipients

Nootropil Tablet 800mg

Nootropil Tablet 1200mg

Macrogol 6000, Opadry Y-1-7000 White, Opadry OY-S 29019 Clear, Sodium Croscarmellose, Colloidal anhydrous silica (Aerosil), Magnesium Stearate

PHARMACEUTICAL FORM

Nootropil Tablet 800mg

White oblong film-coated tablet imprinted with a bisect line and N/N on one side and plain on the other side.

Nootropil Tablet 1200mg

White oblong scored film-coated tablet marked N/N on one side and plain on the other side.

CLINICAL INFORMATION

Indications

Treatment of the elderly with some degree of cerebral functional impairment such as loss of memory, a lack of concentration or alertness and vertigo.

NOOTROPIL is indicated for patients suffering from myoclonus of cortical origin, irrespective of aetiology and should be used in combination with other anti-myoclonic therapies.

Dosage and Administration

Piracetam may be taken with or without food. The film-coated tablets should be swallowed with liquid. It is recommended to take the daily dose in two to four sub-doses.

Route of Administration

For oral use.

Adults

The daily dosage should begin at 7.2g, increasing by 4.8g every three or four days up to a maximum of 24g, in two or three divided 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 1.2g every two days (every three or four days in the case of a Lance- Adams syndrome, in order to prevent the possibility of sudden relapse or withdrawal seizures).

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function *(see Section 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

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

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

Piracetam is contraindicated in:

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

Warnings and 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 a 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.

Excipients

Nootropil Tablet 800mg

Nootropil Tablet 1200mg

Sodium

These products contain about 2 mmol (or about 46mg) sodium per 24g piracetam. This should be taken into consideration by patients on a controlled sodium diet.

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 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.
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 prepartion, there is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.

Adverse Reactions

Clinical Trial and Post Marketing Data

Double-blind placebo-controlled clinical or pharmaco-clinical trials, of which quantified safety data are available, 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 disorder, 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

Piracetam is a “nootrope” that is to say it is a psychotropic agent which acts directly on the brain to improve efficacy of the telencephalon in both normal subjects and those suffering from some functional deficit. This area of the brain is involved in cognition and also has a role to play in learning and memory, in alertness and in consciousness. Piracetam does not produce either sedation or stimulation.
Piracetam can act on the Central Nervous System in a variety of ways. It will modify neurotransmission within the brain, and can help to improve the metabolic environment essential for good neuronal function. It is also a haemorrheological agent and can improve microcirculation without producing vasodilation.

When given as acute or long term treatment for patients suffering from a functional CNS deficit, it will heighten alertness and increase cognitive function. These changes are seen as a significant increase in the alpha and beta activity, with a reduction in delta activity, on an EEG trace.
Piracetam will protect and restore cognitive functional capacity after cerebral trauma such as hypoxia or intoxication, and after electroshock therapy.
Piracetam may be given alone, or together with other drugs when treating cortical myoclonia.
NOOTROPIL will reduce the duration of vestibular nystagmus.
Piracetam will improve regional oxygen and glucose uptake in the brain in patients suffering from dementia subsequent to multiple infarcts, or in those with cerebral ischaemia.
Piracetam will inhibit the increased aggregation of activated platelets and, in conditions where there is abnormal rigidity of the red blood cell, it can restore deformability and the ability to pass through the microvasculature.

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 twice daily, 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 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

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)*. 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.

Other patient characteristics

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, 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.

Clinical Studies

see Section Pharmacodynamic effects

NON-CLINICAL INFORMATION

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 viv*o studies have shown no potential for genotoxicity and carcinogenicity.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date is indicated on the packaging.

Storage

Nootropil Tablet 800mg: Store below 30°C.
Nootropil Tablet 1200mg: Store below 30°C.

Nature and Contents of Container

Pack Sizes

Nootropil Tablet 800mg, box of 90 film-coated white tablets, in thermoformed blister packs or child-resistant (CR) blister packs.
Nootropil Tablet 1200mg, box of 20 film-coated white tablets, in thermoformed blister packs or child-resistant (CR) blister backs

Incompatibilities

None known

Use and Handling

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

Manufactured by:

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Belgium

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