SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nootropil (piracetam) 800 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 mg piracetam
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, oblong, film-coated tablet, with a bisect line, marked N/N

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nootropil is suggested for the symptomatic improvement of memory disorders and intellectual disorders that can be regarded as pathological, in the absence of a diagnosis of dementia.

Nootropil may diminish cortical myoclonus in some patients. To test the sensitivity to piracetam, a trial treatment may therefore be undertaken for a limited duration.

In children for the treatment of dyslexia, in combination with appropriate measures such as speech therapy.

4.2 Posology and method of administration

Symptomatic treatment of memory and / or intellectual disorders

Starting treatment: 4.8 g per day in several doses for the first weeks of the treatment; then a maintenance treatment of 2.4 g per day in two or three doses, possibly reducing to 1.2 g per day.

Treatment of cortical myoclonus

The initial dosage is 24 g of piracetam per 24 hours for 3 days.
If there is no or little response by the 3rd day, continue administering 24 g of piracetam until the 7th day. If the response remains zero or insufficient, stop the treatment on the 7th day. From the day when the dose of 24 g is shown to be active, reduce it by 1.2 g every 2 days, until the myoclonus symptoms reappear. This will indicate the average active dose.
The dose daily of piracetam will be administered in 2 or 3 doses. Treatment with other anti-myoclonic drugs will be maintained at the same dosage.
Then, depending on the clinical benefit obtained, the doses of the other anti-myoclonic drugs will be reduced if possible.
Once started, piracetam treatment will have to be continued as long as the pathology of cerebral origin persists.

Nevertheless every 6 months reduction or withdrawal of the drug treatment should be attempted. The treatment should be stopped by reducing the dose of piracetam by 1.2 g every 2 days to avoid an abrupt flare-

up of the condition (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).

Children

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 sub-doses.

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function (see '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 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:

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

Group	Creatinine clearance (ml/min)	Posology and frequency
Normal	> 80	usual daily dose, 2 to 4 sub-doses
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 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 'Renal impairment' above).

Method of administration

Piracetam should be administered orally and may be taken with or without food. The tablets should be swallowed with liquid. It is recommended to take the daily dose in two to three sub-doses.

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 should not be used in patients suffering from Huntington’s chorea

4.4 Special warnings and precautions for use

Effects on platelets aggregation

Due to the effect of piracetam on platelet aggregation (see section 5.1 Pharmacodynamic properties), 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 aspirin.

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

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 'Posology').

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

Warnings related to the excipients:

This product contains 46 mg sodium per 24 g piracetam equivalent to 2.3% 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

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

Acenocourmarol
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.

Pharmacokinetics 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 Ki 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.

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.

4.6 Pregnancy and lactation

Pregnancy
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 (see section 5.3 Preclinical safety data).
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, when benefit exceeds the risks and the clinical conditions of the pregnant mother treatment with piracetam.

Lactation
Piracetam is excreted in human breast milk. Therefore, piracetam should be avoided 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 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. Summary of safety profile

Double-blind placebo-controlled clinical or pharmacoclinical 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.

b. Tabulated list of adverse reactions

Undesirable effects reported in clinical studies and from post-marketing experience are listed in the following table per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).
Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

Blood and Lymphatic 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

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

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 at http://www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

Symptoms
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. Bloody diarrhoea with abdominal pain, was most probably related to the extreme high dose of sorbitol contained in the used formulation.

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 haemodialysis. 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 characterized 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.

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.

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 anemia, 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 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 prostacyclin 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 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 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.

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.

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, 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 section 4.2 “Posology”).

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”).
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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Macrogol 6000
Colloidal anhydrous silica
Magnesium stearate
Sodium croscarmellose

Film-coating
Hydroxypropyl methylcellulose
Titanium dioxide (E171)
Macrogol 400
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Thermoformed PVC/aluminium blister strips placed into cardboard box containing 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Advanz Pharma Limited
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8. MARKETING AUTHORISATION NUMBER(S)

MA1603/00101

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Date of First Authorisation: 24th November 2006
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10. DATE OF REVISION OF THE TEXT

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