SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nootropil 1200 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1200mg of piracetam
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
The daily dosage should begin at 7.2 g increasing by 4.8 g every three to four days up to a maximum of 24 g, divided in two or three 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 1.2 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).

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.

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:

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

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

Patients with 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 'Dosage adjustment in patients with renal impairment' above).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or other pyrrolidone derivatives.

Piracetam is contra-indicated in patients with severe renal impairment (renal creatinine clearance of less than 20 ml per minute). It is also contraindicated in patients with cerebral haemorrhage and in patients suffering from Huntington's Chorea.

4.4 Special warnings and precautions for use

Effects on platelet aggregation

Due to the effect of piracetam on platelet aggregation (see section 5.1), 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 cerebro-vascular accident (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 4.2).

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).

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

Warnings related to the excipients
This medicine contains less than 1 mmol sodium (23 mg) per 12.6 g, that is to say essentially '*sodium-free'*. When the dose is greater than 12.6 g it cannot be considered 'sodium-free' and it should be taken into consideration by patients on a controlled sodium diet. At maximum daily dose (24 g) this medicine contains 46 mg of sodium. This is equivalent to 2.3% of the recommended maximum daily dietary intake of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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 1422µg/ml.

At 1422µg/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 1422µg/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 20g 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 1.6g oral dose of piracetam.

4.6 Fertility, 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).

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 condition of the pregnant mother requires treatment with piracetam.

Breast-feeding

Piracetam is excreted in human breast milk. Therefore, 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.

Fertility

There are no available clinical data on the effect of piracetam on fertility. Animal studies indicate that piracetam has no effect on fertility in male or female rats.

4.7 Effects on ability to drive and use machines

In clinical studies, at dosages between 1.6 - 15 grams per day, hyperkinesia, somnolence, nervousness and depression were reported more frequently in patients on piracetam than on placebo. There is no experience on driving ability in dosages between 15 and 20 grams daily. Caution should therefore be exercised by patients intending to drive or use machinery whilst taking piracetam.

4.8 Undesirable effects

a. Summary of safety profile

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.

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 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

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 Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard

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. 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.

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

Mechanism of action
Piracetam's mode of action in cortical myoclonus is as yet unknown.

Pharmacodynamic effects
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 ßTG 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 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.

5.2 Pharmacokinetic properties

Absorption

Piracetam is rapidly and almost completely absorbed. Peak plasma levels are reached within 1.5 hours after administration. The extent of oral bioavailability, assessed from the Area Under Curve (AUC), is close to 100% for capsules, tablets and solution. Peak levels and AUC are proportional to the dose given.

Distribution

The volume of distribution of piracetam is 0.7 L/kg. Piracetam crosses the blood-brain and the placental barrier and diffuses across membranes used in renal dialysis.

Biotransformation

Up to now, no metabolite of piracetam has been found.

Elimination

Piracetam is excreted almost completely in urine and the fraction of the dose excreted in urine is independent of the dose given. Excretion half-life values are consistent with those calculated from plasma / blood data. The plasma half-life is 5.0 hours, in young adult men. Clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 6000.
Colloidal anhydrous silica.
Magnesium stearate
Sodium croscarmellose
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

None

6.5 Nature and contents of container

Blister pack in an outer cardboard carton (60 tablets per carton).

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

UCB Pharma Ltd.
208 Bath Road
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SL1 3WE

8 MARKETING AUTHORISATION NUMBER(S)

PL 00039/0536

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10 DATE OF REVISION OF THE TEXT

24/05/2022