SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

BIOTROPIL 800, 800 mg, film-coated tablets
BIOTROPIL 1200, 1200 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Biotropil 800
Each film-coated tablet contains 800 mg of piracetam (*Piracetamum*).

Excipient with known effect: lactose monohydrate 13,20 mg

Biotropil 1200
Each film-coated tablet contains 1200 mg of piracetam (*Piracetamum*).

Excipient with known effect: lactose monohydrate 19,80 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Biotropil 800
Film-coated, longitudinal, white, biconvex tablets, with smooth surface, with a score line on one side, without spots and chips.

Biotropil 1200
Film-coated, longitudinal, white, biconvex tablets, with smooth surface, with a score line on one side, without spots and chips.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Biotropil is indicated:

in adult patients
- suffering from myoclonus of cortical origin;
- to treat dizziness of central and peripheral origin;

in pediatric patients
- in the treatment of dyslexia, in combination with speech therapy.

4.2 Posology and method of administration

Method of administration

- Biotropil should administered orally.
- The tablets should be swallowed with liquid.
- The tablets should not be chewed.
- The tablets may be taken with or without food.
- The tablets should be taken at the same time.

Posology

It is recommended to administer the daily dose in 2 or 3 divided doses.
The daily doses for various indications are presented below.

Adults

Treatment of myoclonus of cortical origin
The daily dosage should begin at 7,2 g increasing to 4,8 g every 3 to 4 days up to maximum of 24 g. The daily dose should be divided into 2 or 3 doses.

In combined treatment with other antimyoclonic drugs their doses should be within the recommended therapeutic doses. If clinical improvement is achieved and it is possible, the doses of other drugs should be reduced.

In people with myoclonus symptoms may evolve 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, in order to prevent the possibility of sudden relapse or withdrawal seizures.

Treatment of dizziness of central and peripheral origin
The daily dose 2,4 g of Biotropil in 3 divided doses per 0,8 g for 8 weeks.

Pediatric population

Treatment of dyslexia, in combination with speech therapy
Children from 8 to 13 years old: the daily dose 3,2 g in 2 divided doses concomitantly with speech therapy.

Special patient groups

Elderly patients
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
Piracetam is eliminated via the kidneys therefore, caution should be exercised in patients with renal insufficiency. In these patients there is an inverse relationship between the half-life and creatinine clearance.

The table below presents recommended dose adjustment. To use this dosing table, an estimate of the patient's creatinine clearance (Cl_{cr}) in ml/min is needed. The creatinine clearance may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$Cl_{cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \text{ (x 0,85 for women)}$$

Group	**Creatinine clearance (ml/min)**	**Posology and frequency**
Normal	≥80	usual daily dose, divided in 2 to 4 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.

Patients with hepatic and renal impairment
The adjustment of dose is recommended (see "Dosage adjustment in patients with renal impairment" above).

4.3 Contraindications

- Hypersensitivity to the piracetam, other pyrrolidone derivatives or to any of the excipients listed in section 6.1
- cerebral hemorrhage
- severe renal impairment
- 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 hemorrhage, patients at risk of bleeding such as gastrointestinal ulcer, patients with underlying disorders of hemostasis, patients with history of hemorrhagic cerebro-vascular accident (CVA), patients undergoing major surgery including dental surgery.

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

Elderly patients
For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adjustment if needed (see section 4.2).

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

Excipients

Lactose monohydrate
Biotropil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
Biotropil contains about 1,5 to 3 mmol (or 35 to 70 mg) sodium per 24 g piracetam. To be taken into consideration by patients with impaired renal function and 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 ($T_3 + T_4$).

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 (ßTG)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 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal 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 70-90% 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 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.

4.7 Effects on ability to drive and use machines

Analysis of the adverse reactions occurring during treatment with piracetam indicates that the drug may affect the ability to drive and use machines. This should be considered.

4.8 Undesirable effects

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.

An ordered list of adverse reactions
Undesirable effects reported in clinical studies and from post-marketing experience are listed below in per System Organ Class and per frequency.

In clinical trials 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: hemorrhagic disorders

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, diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders
Not known: angioneurotic edema, 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 Pharmacovigilance

Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products:
Al. Jerozolimskie 181C
02-222 Warsaw
Tel.: + 48 22 49 21 301
Fax: + 48 22 49 21 309
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4.9 Overdose

Symptoms
One case of bloody diarrhea with abdominal pain, associated with the oral intake of 75 g piracetam daily was reported.
No additional adverse events specifically related to overdose have been reported with the medicine.

Management of overdose
In acute, significant overdose, 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 dialyzer is 50-60% for piracetam.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nootropics,
ATC code: N 06 BX 03

Mechanism of action

The active substance is piracetam (2-oxo-1-pirolidynoacetamide), belonging to the group of pyrrolidone, ring derivative of gamma aminobutyric acid (GABA). Available data suggest that the primary mechanism of action of piracetam is not specific to a particular type of cell or organ. In phospholipid membrane models, piracetam binds physically, proportionally to the dose, with the polar group, initiating the reconstruction of the membrane structure by forming mobile complexes of drug molecules and phospholipids. This probably improves membrane stability so that the membrane or transmembrane proteins maintain or regain an appropriate three-dimensional structure that allows them to perform their normal functions.

Piracetam acts on nerve cells and the vascular system.

Piracetam has various effects on the cell membranes of nerve cells (neurons).
In animals, piracetam enhances various neuronal signaling processes, primarily by modulating the density and function of postsynaptic receptors.

Piracetam modifies the rheological properties of blood by affecting platelets, red blood cells, and the walls of blood vessels. Piracetam increases erythrocyte elasticity and reduces platelet aggregation, reduces erythrocyte adhesion to blood vessel walls and capillary spasm.

Pharmacodynamic effects

Effects on 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 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 red blood cells 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.
In another study in healthy volunteers, there were no statistically significant differences between piracetam (up to 12 g twice daily) and placebo in terms of effect on hemostasis and bleeding time.

5.2 Pharmacokinetic properties

The pharmacokinetics of piracetam is linear and does not change over time. Low inter-individual variability was found in studies in a wide range of doses. Such data confirm high permeability, solubility and minimal metabolism. The elimination half-life of piracetam in plasma is 5 hours. Similar values were determined in adult volunteers and patients. The elimination half-life increases in the elderly (mainly due to decrease in renal clearance) and in people with impaired renal function. Piracetam reaches a steady-state concentration within 3 days of starting administration.

Absorption
Piracetam is rapidly and almost completely absorbed. When taken on an empty stomach, it reaches peak plasma concentration one hour after administration. The absolute bioavailability of oral dosage forms is close to 100%. Food has no effect on the extent of absorption but reduces the value of C_{max} by 17% and increase value of t_{max} from 1 h to 1,5 h. The highest plasma concentration is usually 84 µg/ml after a single oral dose of 3,2 g and 115 µg/ml after multiple doses 3,2 g tid.

Distribution
Piracetam is not bound to plasma proteins. The volume of distribution is approx. 0,6 l/kg.
Piracetam crosses the blood-brain barrier and can be detected in the cerebrospinal fluid after intravenous administration. The t_{max} value in cerebrospinal fluid is approx. 5 h and half-life approx. 8,5 h. In animals, the highest levels of piracetam in the brain were found in the cerebral cortex (in the frontal, parietal and occipital lobes), in the cerebellum and the basal ganglia. Piracetam penetrates all tissues except adipose tissue, crosses the placental barrier and the cell membranes of isolated erythrocytes.

Biotransformation
There is no evidence that piracetam is metabolized in the body. The significantly increased plasma half-life in patients with anuria and the detection of the majority of the taken dose of piracetam in urine confirms the lack of metabolism.

Elimination
The plasma half-life of piracetam in adults is approximately 5 h. The total body clearance is 80-90 ml/min. Piracetam is mainly excreted in the urine (80-100% of the dose). Elimination occurs by glomerular filtration.

Linearity/non-linearity
The piracetam' pharmacokinetics linearity was found within the dose range 0,8 to 12 g. Pharmacokinetic parameters, such as half-life and clearance, do not change depending on the dose and duration of treatment.

Pharmacokinetics in various patient groups

Sex
In a bioequivalence study of the different dosage forms of the medicine in the strength 2,4 g was found that values of C_{max} and AUC were approx. 30% higher in women (N=6) than in men (N=6). At the same time, the clearance values after comparisons of body weight differences were found.

Elderly
The elimination half-life of piracetam is prolonged in the elderly, which is associated with the decrease in renal function in this patient group (see section 4.2).

Pediatric population
The pharmacokinetics of piracetam has not been studied in children.

Renal impairment
Piracetam clearance is correlated with creatinine clearance. Therefore, it is recommended that the daily dose of piracetam be adjusted in patients with impaired renal function according to creatinine clearance (see section 4.2).
In people with anuria in the end-stage of renal failure, the half-life of piracetam is increased to 59 hours. 50-60% piracetam was removed during a typical 4-hour dialysis session.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of piracetam has not been studied. Because 80-100% of the dose is excreted in the urine, it is not expected that only due to hepatic impairment there will be a significant change in piracetam excretion.

5.3 Preclinical safety data

Data from non-clinical studies indicate low potential toxicity to piracetam. No irreversible toxic effects were observed after single doses (10 g/kg in mice, rats and dogs). Repeated dose and chronic toxicity studies in mice (up to 4,8 g/kg/day) and rats (up to 2,4 g/kg/day) did not show organ toxicity. Mild gastrointestinal disorders (vomiting, change in fecal consistency, increased water intake) were observed in dogs given piracetam for one year at increased doses of 1 to 10 g/kg/day. Intravenous administration of doses up to 1 g/kg/day for 4-5 weeks in rats and dogs also did not lead to toxic side effects.
In the *in vitro* and *in vivo* studies no genotoxic or carcinogenic effects were found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core of the tablet:
Macrogol 6000
Lactose monohydrate
Sodium croscarmellose
Magnesium stearate

Film-coating of the tablet:
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Biotropil 800
The PVC/ PVDC/Aluminum blisters in a carton box.

Package size:
60 film-coated tablets (6 blisters of 10 tablets)
60 film-coated tablets (4 blisters of 15 tablets)

Biotropil 1200
The PVC/ PVDC/Aluminum blisters in a carton box.

Package size:
60 film-coated tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biofarm Sp. z o.o.
Wałbrzyska str. 13
60-198 Poznań, Poland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT