SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEBROTONIN 800 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 800 mg piracetam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets for oral administration.
CEBROTONIN 800 mg film-coated tablets are oblong coated tablets with breaking notch, slightly yellow to beige in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEBROTONIN is indicated in adults from 18 years of age.

Symptomatic treatment of chronic cerebro-organically conditioned disturbances of functional capacity in the course of a therapeutic overall programme in case of syndromes of dementia becoming manifest as: impaired memory, lack of concentration, blocking of thought processes, premature fatigue and lack of drive and motivation, affective disturbances. The individual response to the medication cannot be forecast.

Hint:
Before beginning the treatment with this product, it should be clarified whether the symptoms are not due to a basic disease which has to be treated specifically.

4.2 Posology and method of administration

Posology

The dosage depends on type and severity of the clinical picture and the patient's response to the therapy. Following dosage guidelines apply:

For adults: 3 times daily 1 film-coated tablet of this product (equivalent to 2.4 g piracetam).
On special medical prescription the dose can be raised to 3 times daily 2 film-coated tablets of this product (equivalent to 4.8 g piracetam).

Dose adjustment in elderly patients
Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Dose adjustment in patients with impaired renal function"). Periodic monitoring of creatinine clearance is required during long-term treatment of elderly patients to adjust the dose if needed.

Dose adjustment in patients with impaired renal function

As piracetam is exclusively eliminated via the kidneys, increased plasma levels may be produced in case of reduced renal function. The daily dose must therefore be adjusted according to the patient's 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:

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

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 to 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

Dose adjustment in patients with impaired liver function

Piracetam is not metabolised in the liver. For patients with reduced liver function no dosage adjustment is needed. In patients with impaired liver as well as impaired renal function dosage, dosage adjustment is recommended (see "Dose adjustment in patients with impaired renal function").

Pediatric population

The safety and efficacy of CEBROTONIN in children aged below 18 years of age have not been established.

Method of administration

This product should be taken with one glass of liquid (e. g. water), for reasons of expediency together with or directly after the meals.

The duration of treatment depends on the physician's decision.

In case of a supporting treatment of syndromes of dementia it has to be verified after three months whether a further treatment is still indicated.

4.3 Contraindications

CEBROTONIN must not be used in the following cases:

- in case of known hypersensitivity to piracetam, other pyrrolidone derivates or to any of the excipients listed in section 6.1.
- in case of cerebral haemorrhage (e. g. stroke).
- in case of severe renal insufficiency (renal insufficiency at terminal stage).
- in case of suffering from the genetic disease Huntington's chorea.

4.4 Special warnings and precautions for use

Before beginning the treatment with this product, it should be clarified whether the symptoms are not due to a basic disease which has to be treated specifically.

Caution should be taken in the following cases:
- Piracetam may only be used with due consideration of all necessary precautionary measures in case of psychomotor restlessness.
- 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.
- Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency (see section 4.2). In elderly patients who take CEBROTONIN for a longer period, it is necessary to regularly check the values of creatinine clearance to adjust the dose if needed (see section 4.2).
- patients who are taking medicines for seizures (anticonvulsants), should keep the treatment with anticonvulsants, even if they think their condition has improved since taking CEBROTONIN.
- doping Note: The use of CEBROTONIN can lead to positive results in doping controls.

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 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.

Due to the mechanism of action, synergistic interactions with other CNS-stimulating drugs (due to the intensification of hyperkinesis) can occur.

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.

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.
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 passes over to the mother's milk. This product should therefore not be taken during breast-feeding or alternatively breast-feeding should be discontinued during CEBROTONIN treatment. 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

Due to observed adverse reactions a possible impairment of reactivity cannot be excluded.
Patients should thus avoid driving vehicles or operating machinery until the effects have worn off.

4.8 Undesirable effects

a. Summary

Double-blind placebo-controlled clinical and 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	(≥1/1000 <1/100),
Rare	(≥1/10 000 <1/1000),
Very rare	(<1/10 000),
Not known	(frequency cannot be estimated from the available data)

Blood and lymphatic system disorders
Not known: hemorrhagic disease

Immune system disorders
Very rare: allergic reactions such as anaphylactic reactions

Not known: hypersensitivity

Metabolism and nutrition disorders
Common: weight gain

Psychiatric disorders
Common: increased psychomotor activity, nervousness, aggressiveness, disturbed sleep, insomnia, depressive mood, anxiety
Uncommon: depression
Very rare: states of confusion, hallucinations

Nervous system disorders
Common: excessive motor activity (hyperkinesia)
Very rare: drowsiness (somnolence), headaches, disturbances in the interaction of movements (ataxia), impaired balance
Not known: exacerbation of epilepsy, sleeping disorders

Ear and labyrinth disorders
Uncommon: dizziness

Vascular disorders
Uncommon: blood pressure reduction or enhancement

Gastrointestinal disorders
Common: gastrointestinal discomfort (abdominal discomfort), diarrhea, nausea, vomiting
Not known: abdominal pain, upper abdominal pain, dry mouth, increased salivation

Skin and subcutaneous tissue disorders
Very rare: skin redness and flushing, sweating, itching, hives (urticaria)
Not known: painful swelling of the skin and mucous membranes (Oedema Quincke's), inflammatory skin reaction (dermatitis)

General disorders and administration site conditions
Uncommon: weakness or loss of strength (asthenia), increased sex drive (libido increase), increased sexuality

The side effects in adults were reported in case of doses of approx. 5 g piracetam per day. In children, comparable side effects were observed in case of dosages of approx. 3 g piracetam per day. In case of side effects the physician has to be informed.

Hint:
The desired synchronisation and support of the electric activity of the brain can in exceptional cases lead to a decrease in the convulsion threshold in specially disposed patients (neuronal hyperexcitability).
It should be taken care that patients who need anticonvulsants maintain this therapy even if the treatment with this product results in a subjective improvement.

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 to WALTER RITTER GmbH + Co. KG:

WALTER RITTER GmbH + Co. KG
Spaldingstr. 110 B

20097 Hamburg
GERMANY
E-Mail: drugsafety@walterritter.com

4.9 Overdose

Symptoms
There are no documented cases of further adverse reactions (see section 4.8) which occurred after an overdose of 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 case of acute and significant overdose it is possible to empty the stomach by gastric irrigation or by causing vomiting. There is no specific antidote for piracetam. The treatment is only symptomatic and may also include hemodialysis. The extraction coefficient for piracetam is 50 - 60%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nootropics, ATC code: N06BX03

In animal experiments, the decreased brain metabolism is improved with piracetam by stimulating the oxidative breakdown of glucose via the pentose phosphate pathway, increasing the ATP turnover, increasing the cAMP concentration in the neurons, stimulating the adenylate kinase, stimulating the phospholipid metabolism with increased incorporation of ^{32}P in phosphatiylcholine and -inositol. Promotion of protein biosynthesis and synthesis or turnover rate of the respiratory ferment cytochrome b5 under hypoxia.

Piracetam causes an increase in the density of m-cholino receptors and an increase in dopamine turnover in older animals. It favors the transmission and conduction of excitation in the different brain regions with an improvement in the EEG performance spectrum.

EEG examinations showed an increase in the alpha components with a simultaneous reduction in the theta and delta components.

Piracetam affects the impaired learning and memory function in the patient.

In addition, piracetam has hemostasiological and -rheological effects by improving erythrocyte deformability, decreasing erythrocyte aggregation, lowering plasma viscosity, decreasing flow shear stress and inhibiting platelet aggregation.

5.2 Pharmacokinetic properties

Piracetam is rapidly and completely absorbed after oral administration. The relative systemic bioavailability compared with AUC values after intravenous administration is 100% (800 mg piracetam as a single dose). Cmax is reached after 30 min (tmax) and is 15-19 µg / ml. Irrespective of the type of application, the half-life in the plasma is on average 5.2 h (4.4 - 7.1 h) or 7.7 h in the cerebrospinal fluid. According to in vitro studies, about 15% of piracetam is bound to plasma protein.

The volume of distribution is around 0.6 l / kg. The total plasma clearance is approx. 120 ml / min. Metabolites have not yet been found.

In the case of renal insufficiency, excretion is delayed, so that a dose reduction according to the residual nitrogen or creatinine values is necessary to avoid accumulation effects. Piracetam is 50-60% dialysable.

Piracetam crosses the placental barrier and is detectable in the fetal plasma and in the amniotic fluid (43 patients; 2.4 or 6 g piracetam 2 to 3 hours before birth). The concentration in the fetal plasma was approx. 10-30% lower than that in the maternal. Regardless of the dose, the plasma half-life in newborns was 200 min, almost twice as long as that of the mother (98-112 min). Piracetam is excreted in breast milk.

Bioavailability
Piracetam is 100% bioavailable when taken orally.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

povidone
colloidal anhydrous silica
magnesium stearate
talc
hypromellose
propylene glycol
macrogol 6000
colouring agents titanium dioxide, ferric oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
After its expiry this preparation must not be applied any more.

6.4 Special precautions for storage

Store in a dry place at a temperature of max. 30°C.
Protect from sunlight.

6.5 Nature and contents of container

Original package contains 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

WALTER RITTER GmbH + Co. KG
Spaldingstr. 110 B
20097 Hamburg
GERMANY
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8. MARKETING AUTHORISATION NUMBER(S)

FDA/SD.203-01006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 1st February 2020

10. DATE OF REVISION OF THE TEXT

March 2021

PRESCRIPTION AND PHARMACY-ONLY
Prescription and pharmacy-only