SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VICEBROL FORTE, 10 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains vinpocetine 10 mg.

Excipient with known effect: lactose monohydrate 200.6 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablets, of smooth surface, with a breakline on one side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- symptomatic treatment of chronic cerebral blood circulation disorders, occurring as a result of a stroke (memory impairment, decrease in intellectual efficiency, ataxia),
- treatment of psychical and neurological symptoms of cerebral blood circulation disorders in course of atherosclerosis of cerebral arteries, including vascular dementia,
- auxiliary treatment of vascular eye diseases,
- auxiliary treatment of vascular ear diseases.

4.2 Posology and method of administration

Posology

Adults
The recommended dose is 1 tablet 3 times a day (30 mg/day).

The therapeutic activity of vinpocetine begins approximately after a week, the maximum therapeutic activity is reached within 3 months, and improvement of the clinical state can be seen after 6-12 months of treatment.

Elderly
Dosage adjustment is not necessary (see section 5.2).

Patients with impaired renal and (or) hepatic function
Doses should be reduced in patients with severe renal failure (see section 4.4).
No dosage adjustment is necessary in the rest of patients with hepatic and (or) renal function impairment.

Children and adolescents
Vinpocetine should not be used in children and adolescents due to insufficient data on safety and efficacy in this group of patients (see section 4.3).

Method of administration
The tablets should be taken orally, after a meal.
The tablets should be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe ischaemic heart disease and cardiac arrhythmia.
- Bleeding to central nervous system (CNS) (e.g. intracerebral hemorrhage, acute phase of hemorrhagic stroke).
- Pregnancy and lactation.
- In children and adolescents – due to lack of sufficient data on the use of vinpocetine in this group of patients.

4.4 Special warnings and precautions for use

In patients with advanced renal failure the dose of vinpocetine should be reduced.

In case of fall in blood pressure or abnormal heart rhythm, the product should be discontinued.

It is recommended to control the ECG in case of a long QT syndrome or when another drug is used, which causes the long QT interval.

Excipients
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been observed in case of the administration of vinpocetine with beta-adrenolytic drugs such as chloranolol and pindolol, with clopamide or hydrochlorothiazide.

No interactions observed with digoxin and acenocoumarol.

A combined therapy with vinpocetine did not pose a risk of interactions with other drugs in case of the treatment of diabetes with glibenclamide.

Vinpocetine administered concomitantly with adenosine increased its neuroprotective effects.

In rare cases vinpocetine increased the hypotensive activity of α-methylodopa, therefore regular blood pressure control is recommended during such combined therapy.

Caution is recommended when vinpocetine is used concomitantly with CNS drugs, antiarrhythmics and anticoagulants.

4.6 Fertility, pregnancy and lactation

Vinpocetine is contraindicated to use during pregnancy and breastfeeding.

Pregnancy
Vinpocetine penetrates the placenta, but reaches lower concentration in the placenta and the foetal blood than in the mother's blood. No teratogenic or embyotoxic effect has been observed in pregnant women. In animal studies, when high doses were administered, bleeding from the placenta and miscarriage have been found in few cases (probably due to the increased placental flow).

Breastfeeding
Vinpocetine is contraindicated to use during lactation, because it passes to the mother's milk.
Studies using the radiolabelled products demonstrated that reaches a radioactivity 10 times higher in the mother's milk than in her blood. 0.25% of the radiolabelled drug dose is excreted into mother's milk within one hour.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive vehicles and use machines have not been investigated.
The decision about the possibility of driving vehicles or using machinery should be taken by doctor.

4.8 Undesirable effects

Adverse effects have been ranked according to System Organ Class and under headings of frequency using the following convention:

- very common: ≥1/10
- common: ≥ 1/100, <1/10
- uncommon: ≥ 1/1000, <1/100
- rare: ≥ 1/10000, <1/1000
- very rare: <1/10000
- not known: cannot be estimated from the available data

Blood and lymphatic system disorders
Rare leucopoenia.

Nervous system disorders
Uncommon sleep disorders (insomnia, somnolence), vertigo, headaches, asthenia, tingling sensation in limbs, sweating, motor hyperactivity.
The adverse effects may also be related with basic disease.

Cardiac disorders
Uncommon: reduction of the ST segment, lengthening of the QT interval, tachycardia and ectopic beats.

Vascular disorders
Uncommon: change of the arterial blood pressure (mainly decrease in blood pressure), face reddening (flushing).

Gastrointestinal disorders
Uncommon : nausea, heartburn, dryness of the oral mucosa.

Hepatobiliary disorders
Uncommon : elevated level of hepatic enzymes.

Skin and subcutaneous tissue disorders
Uncommon : allergic skin reactions.

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, Poland
Tel.: + 48 22 49 21 301
Fax: + 48 22 49 21 309
e-mail: ndl@urpl.gov.pl

4.9 Overdose

No cases of overdose have been reported.

Long-term use of vinpocetine in dose of 60 mg is safe. Adverse reactions do not occur even after using a single dose 6 times higher than the dose recommended in the clinical practice (ca. 360 mg).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics; other psychostimulants and nootropics.
ATC code: N06BX18

Mechanisms of therapeutic action of vinpocetine are complex. It beneficially influences the metabolism of cerebral tissue, improves cerebral blood flow and rheological properties of blood.

Vinpocetine exerts a protective effect on nervous tissue: it mitigates harmful effects of cytotoxic reactions evoked by aminoacids. Vinpocetine blocks sodium and calcium channels depending on its concentration and inhibits MNDA and AMPA receptors activity.
Vinpocetine increases the neuroprotective effect of adenosine.

Vinpocetine stimulates cerebral metabolism: it increases glucose and oxygen usage by cerebral tissue; improves cerebral cells tolerance to hypoxia; increases glucose (the sole energy source for brain) transport through the brain-blood border; changes the glucose metabolism to more efficient aerobic metabolic pathways; by selective inhibition of Ca^{2+} /calmodulin-dependant cyclic 3',5'-guanosine monophosphate phosphodiesterase (cGMP-PDE) activity, the drug indirectly increases cerebral levels of cAMP and cGMP and leads to relaxation of smooth muscles in cerebral blood vessels.
Vinpocetine increases ATP (adenosine triphosphate) level and ATP/AMP (adenosine triphosphate/ adenosine 5'-monophosphate) ratio in the brain; initiates intensive aerobic metabolism of glucose in the brain; increases cerebral metabolism of noradrenaline and serotonine; stimulates the adrenergic system and exerts antioxidant effect. As a result, vinpocetine exerts a protective effect on the brain.

Vinpocetine improves cerebral microcirculation: it inhibits platelet aggregation; reduces the pathologically increased blood viscosity; increases erythrocyte (red blood cells) deformability and inhibits adenosine (one of the most important local blood flow regulator) uptake by erythrocytes; facilitates oxygen transport into cerebral tissue by reducing the oxygen affinity of erythrocytes.

Vinpocetine selectively increases blood flow in cerebral vessels: it increases the share of the brain in cardiac output; it reduces cerebral vascular resistance without affecting systemic circulation (blood pressure, heart rate, cardiac output, total peripheral resistance).

Vinpocetine does not elicit steal phenomenon. On the contrary, it primarily improves the blood supply of the injured, ischaemic area while it remains unchanged in the intact areas (inverse steal effect), itfurther increases blood flow which is already increased as a result of hypoxia.

5.2 Pharmacokinetic properties

Absorption
Vinpocetine is fast absorbed and after oral administration it reaches maximum plasma concentration within 1 hour. Vinpocetine is mainly absorbed in the upper gastrointestinal tract. Total bioavailability of vinpocetine after oral administration is 7%.

Distribution
In human: the plasma protein bond is 66%. Volume of distribution is 246,7 ± 88,5 l, which indicates significant binding within tissues
Vinpocetine was orally administrated to rats in radiolabelled studies and the maximum drug concentration has been found in the liver and gastrointestinal tract. Maximum concentration in tissues was determined 2-4 hours after administration of vinpocetine. The concentration of radiolabelled viinpocetine in the brain have not exceed that found in the blood.

Biotransformation
The main metabolite of vinpocetine is apovincaminic acid (AVA), which comprises 25-30% of all metabolites in human. After oral dose area under the curve for AVA is 2-fold higher than after intravenous dose, which means AVA production in the liver during the first passage of vinpocetine. The other metabolites are: hydroxyvinpocetine, hydroxyl-AVA, dihydroxy-AVA-glicynate their glucuronide and sulphate conjugates.
Total plasma clearance of vinpocetine (66,7 l/h) is higher than hepatic clearance (50 l/h), which shows extrahepatic metabolism of vinpocetine.
In animal studies only several percent of vinpocetine in unchanged form has been excreted from organism in every species.

Excretion:
After multiply oral administration of 5 mg and 10 mg of vinpocetine, it has been found that steady-state plasma concentrations were 1,2 ± 0,27 ng/ml and 2,1 ± 0,33 ng/ml, respectively, which means the linear pharmacokinetics of vinpocetine. The biological half-life of vinpocetine in human is 4,83 ± 1,29 hours. Radiolabelled studies have shown that product is excreted mainly with urine (60%) and faeces (40%). In rats and dogs most of the radiolabelled dose have been of bile origin, however, the significant drug concentration in enterohepatic circulation has not been confirmed.
Apovincaminic acid is excreted via kidney by simple glomerular filtration and its biological half-life changes depending on vinpocetine dose and route of administration.

Changes in pharmacokinetic properties in elderly patients and patients with coexisting diseases
Vinpocetine is indicated for the use mainly in the elderly population, in whom changes in pharmacokinetics parameters of the drug are observed (decreased absorption, changes in distribution and metabolism, decreased excretion of the drug), therefore kinetics studies of vinpocetine in this group of patients are very important, especially during long-term treatment with this medicinal product. Results of these studies have shown that pharmacokinetics parameters of vinpocetine in the elderly patients do not differ significantly from a non-elderly adult population and no drug accumulation is observed. Dose adjustment is not necessary in patients with hepatic and renal disorders, because the drug do not accumulate in these group of patients, even during long-term treatment.

5.3 Preclinical safety data

Acute toxicity
Studies concerning acute toxicity of vinpocetine have been carried out in mice, rats and dogs. No oral LD_{50} in dogs has been determined, because dogs did not tolerate doses higher than 400 mg/kg b.w. (vomiting).

Subchronic toxicity
There have been no toxic effects of the drug after intravenous administration doses up to 8 mg/kg b.w. for 14 days in rats. Similar situation has been observed in dogs after intravenous administration doses up to 5 mg/kg b.w. for 28 days. After the higher doses the following adverse reactions have been observed: salivation, increased heart rate and accelerated breathing. Rats tolerated even oral doses up to 25 mg/kg b.w. administered for 28 days.

Chronic toxicity
Studies on chronic toxicity of vinpocetine have been carried out in animals for over 1 year. No pathological effects in clinical state of animals and in laboratory results have been found, e.g. no systemic toxic effects of vinpocetine have been observed in rats taking oral dose of 100 mg/kg b.w. for 6 months. In dogs decreased hunger and vomiting have been found only after taking dose of 45 mg/kg b.w.
The following adverse reactions have been observed in dogs after intravenous administration of the drug in dose higher than 5 mg/kg b.w. for 90 days: decreased hunger, convulsions, increased heart rate and accelerated breathing, while laboratory and histopathological results have been negative.

Studies on the effect on fertility
Results of the studies have shown that vinpocetine has no adverse effect on the fertility of males and females of the tested species. No teratogenic or embryotoxic effect of vinpocetine has been noticed. Bleeding from placenta and miscarriages have been observed in some cases after administering high doses of vinpocetine, probably due to increased placental blood flow.
In pregnant females toxic effect of vinpocetine have been intensified after intravenous administration.
Studies on perinatal and postnatal toxicity of vinpocetine have not shown any toxic effects of the drug on offspring.

Mutagenic activity
No mutagenic effects of vinpocetine have been found in several test methods.

Carcinogenic activity
No carcinogenic effects of vinpocetine have been observed in 2-year studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Starch pregelatinized
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Carton box containing 30 or 90 tablets.

PVC/PVDC/Aluminium blisters placed into a cardboard box.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

09091/10980/NMR/2023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT