

1. NAME OF THE MEDICINAL PRODUCT

Bilobil® 40 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard, contains 40 mg of extract (as dry extract, refined and quantified) from *Ginkgo biloba* L., folium (Ginkgo leaf) (35 - 67 : 1), corresponding to:

- 8.8 to 10.8 mg of flavonoids expressed as flavone glycosides,
- 1.12 to 1.36 mg of ginkgolides A, B, C and
- 1.04 to 1.28 mg of bilobalide.

First extraction solvent: Acetone 60% m/m.

Excipients with known effect:

Each hard capsule contains 62.7 mg lactose, 0.015 mg azorubine (E122) and 2 mg glucose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

Violet-brown capsules. The capsule contains a light to dark brown powder with visible darker particles and possible small clods.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bilobil capsules are a herbal medicinal product that is recommended for symptomatic treatment:

- in disturbances of cerebral circulation and function (syndrome of dementia in primary degenerative dementia, in vascular dementia or in a mixed form of both) manifested as decline in memory and intellectual capacity, vertigo, tinnitus, indisposition, headache and sleep disorders, general malaise;
- in initial disturbances of blood perfusion of the extremities, manifested as cold feet, tingling, numbness or pain on walking.

4.2 Posology and method of administration

Disturbances of cerebral circulation and function (syndrome of dementia in primary degenerative dementia, in vascular dementia or in a mixed form of both):

The recommended dose is 3 capsules once to twice daily.

Initial disturbances of blood perfusion of the extremities:

The recommended dose is 1 capsule three times daily.

The capsules should be swallowed whole with some liquid. They may be taken without regard to meals. Concomitant intake of alcoholic beverages is not advised.

The first signs of improvement are usually observed after one month. For a longer-lasting effect, it is recommended, especially to the elderly, that the capsules be taken for at least three months. After that

period a doctor should be consulted in order to determine whether to continue treatment or to repeat the treatment course. If there is no symptomatic improvement after 3 months, or if pathological symptoms should intensify, the doctor should check whether continuation of treatment is still justified.

In case of a missed dose the medicine should be taken as soon as possible. If, however, it is already the time for the next dose, a double dose should not be taken to compensate for the missed one. Treatment should be continued as usual.

Paediatric population

There is no relevant indication for children and adolescents under 18 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Pregnancy.

4.4 Special warnings and precautions for use

Before the beginning of treatment with Bilobil capsules, it is necessary to confirm that the mentioned symptoms are not a result of another underlying disease that requires specific treatment. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.

Preparations containing *Ginkgo biloba* might increase susceptibility to bleeding. As a precaution, treatment with Bilobil should be discontinued 3 to 4 days prior to surgery.

Patients with an abnormal tendency to spontaneous bleeding (haemorrhagic diathesis) and concomitant anticoagulant or antiplatelet treatment should consult the doctor before starting treatment with Bilobil.

Patients treated with blood sugar- or blood pressure-lowering drugs should consult their doctor before starting treatment with Bilobil.

In patients with epilepsy, onset of further seizures – promoted by intake of *Ginkgo biloba* preparations – cannot be excluded.

Concomitant use of *Ginkgo biloba* containing products and efavirenz is not recommended (see section 4.5).

Paediatric population

Bilobil capsules are not recommended for children under 18 years of age because of limited data on the safety of use in this age group.

Special information about some of the ingredients

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

Bilobil contains azorubine (E122), which may cause allergic reactions. It may have an adverse effect on activity and attention in children.

4.5 Interaction with other medicinal products and other forms of interaction

If the medicinal product is taken concomitantly with anticoagulants (e.g. phenprocoumon and warfarin) or antiplatelet drugs (e.g. clopidogrel, acetylsalicylic acid and other non-steroidal anti-inflammatory drugs), their effect may be influenced.

Available studies with warfarin do not indicate that there is an interaction between warfarin and *Ginkgo biloba* products, but adequate monitoring is advised when starting, when changing *G. biloba* dose, when ending *Ginkgo biloba* intake or if changing product.

An interaction study with talinolol indicates that *Ginkgo biloba* may inhibit P-glycoprotein at the intestinal level. This may give rise to increased exposure of drugs markedly affected by P-glycoprotein in the intestine such as dabigatran etexilate. Caution is advised if combining *Ginkgo biloba* and dabigatran.

One interaction study has indicated that the C_{max} of nifedipine may be increased by *Ginkgo biloba*. In some individuals, increases by up to 100% were observed resulting in dizziness and increased severity of hot flushes.

Concomitant use of *Ginkgo biloba* preparations and efavirenz is not recommended; plasma concentrations of efavirenz may be decreased because of induction of CYP3A4 (see also section 4.4).

4.6 Pregnancy and lactation

Pregnancy

Ginkgo biloba extracts may impair the ability of platelets to aggregate. The tendency for bleeding may be increased. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). The use is contraindicated in pregnancy (see section 4.3).

Breast-feeding

It is unknown whether *Ginkgo biloba* metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. In the absence of sufficient data, the use during lactation is not recommended.

Fertility

No specific studies with *Ginkgo biloba* in humans have been conducted to evaluate effects on fertility. In a study in female mice effects on fertility were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Until now, Bilobil has not been reported to affect the ability to drive and use machines.

4.8 Undesirable effects

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Very common	Common	Not known
Nervous system disorders	headache	dizziness	~~Headache~~
Gastrointestinal disorders		diarrhoea, abdominal pain, nausea, vomiting	
Vascular disorders			Bleeding of individual organs (eye, nose, cerebral, gastrointestinal haemorrhage)
Immune system disorders			hypersensitivity reactions, including allergic shock
Skin and subcutaneous tissue disorders			allergic skin reactions (erythema, oedema, itching and rash)

In case of hypersensitivity, treatment should be discontinued and a doctor consulted.

If severe undesirable effects occur, treatment should be discontinued.

4.9 Overdose

No case of overdose has been reported. There have been no reports of poisoning with quantified ginkgo leaf dry extract in humans.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other anti-dementia drugs, ATC code: N06DX02.

Bilobil capsules contain quantified ginkgo leaf dry extract (*Ginkgo biloba* L.), which belongs to the group of herbal medicines used to treat dementia. Dementia is a chronic progressive disease of the brain, the most pronounced symptom is memory loss.

Ginkgo leaf dry extract improves blood circulation in the brain and also the blood metabolism. This attenuates the loss of mental capacity in mild to moderate dementia of all types.

Additionally, ginkgo leaf dry extract attenuates the symptoms of impaired circulation in the lower limbs, such as the feeling of cold, tingling, numbness and pain when walking.

5.2 Pharmacokinetic properties

Due to the complex composition of ginkgo leaf dry extract, pharmacokinetic studies are difficult to perform.

5.3 Preclinical safety data

Complete preclinical safety data are not available.

Quantified ginkgo leaf extract has a very low acute toxicity. The oral LD₅₀ is more than 5000 mg/kg in mice and rats, the intraperitoneal LD₅₀ is 1900 mg/kg in mice and 2100 mg/kg in rats, whereas the

intravenous LD₅₀ is 1100 mg/kg in both species. No signs of toxicity were observed in an acute toxicity study in mice.

Standardised ginkgo leaf extract showed low toxicity even after repeated administration. Chronic administration to rats was found to reduce glucose utilisation in various brain structures and corticosterone excretion.

Standardised ginkgo leaf extract had no toxic effects on animal reproduction. Reduced sperm penetration into hamster oocytes was seen *in vitro*.

No mutagenic action was observed in the Ames test.

There are no literature data regarding the carcinogenic potential of standardised ginkgo leaf extract.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipient in the herbal preparation

Spray-dried liquid glucose

Capsule contents

Lactose monohydrate

Maize starch

Talc

Colloidal anhydrous silica

Magnesium stearate

Capsule shell

Titanium dioxide (E171)

Indigotin (E132)

Azorubine (E122)

Red iron oxide (E172)

Black iron oxide (E172)

Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in original package in order to protect from moisture.

6.5 Nature and contents of container

Blister pack: 20 capsules (2 blister packs of 10 capsules), in a box.

Blister pack: 60 capsules (6 blister packs of 10 capsules), in a box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT