PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

GINKGOFORCE®

COMPLEMENTARY MEDICINE

Western Herbal Medicine
This medicine has not been evaluated by the South African Health Products Regulatory Authority for its quality, safety or intended use as a Western Herbal Medicine.

SCHEDULING STATUS
S0

1 NAME OF THE MEDICINE
A.VOGEL GINKGOFORCE® (oral drops)
Ginkgo biloba L. *(Ginkgo biloba)*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml contains:

Ginkgo biloba L. (*Ginkgo biloba*) .....915 mg
[Fresh leaves; 1:9 extract providing dry plant equivalent of 101,7 mg per ml drug product]

Contains more than 60 % *v/v* alcohol.
Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Clear, green-brown liquid with fine particles (plant parts), with an aromatic odour.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
A.VOGEL GINKGOFORCE® is a herbal medicine which supports circulation and cognitive health. It is indicated for the supportive treatment of circulatory disorders leading to symptoms such as coldness and discomfort of the extremities and heaviness of the legs. Also for the supportive treatment of mild age associated cognitive impairment (dementia) and its negative impact on quality of life, including symptoms such as forgetfulness, weakness of memory and poor concentration.

4.2 Posology and method of administration
Posology
Adults and children over 12 years:
Take 20 drops 3 times daily.

Special populations
Elderly population:
No dosage adjustment is required for this population.

Paediatric population:
This product is not indicated in patients younger than 12 years.

Method of administration
For oral use only.
Take drops diluted in a small volume of water.
Take 30 minutes before meals.

Duration of use:
Treatment should last for at least 8 weeks.
If there is no symptomatic improvement after 3 months, or if pathological symptoms intensify, consult a doctor to establish if continuation of treatment is justified.

4.3 Contraindications
- A.VOGEL GINKGOFORCE® should not be used in patients who have a hypersensitivity to the active substance, *Ginkgo biloba* L. (*Ginkgo biloba*), or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
- A.VOGEL GINKGOFORCE® contains alcohol and should be used with caution by individuals with a sensitivity or intolerance to alcohol.
- In patients with a pathologically increased bleeding tendency (haemorrhagic diathesis) and concomitant anticoagulant and antiplatelet treatment, the medicinal product should only be used after consultation with a doctor.
- Preparations containing *Ginkgo biloba* might increase susceptibility to bleeding, the medicinal product should be discontinued, as a precaution, 3 to 4 days prior to surgery.
- In patients with epilepsy, onset of further seizures, promoted by intake of *Ginkgo biloba*, cannot be excluded.
- Concomitant use of A.VOGEL GINKGOFORCE® and efavirenz is not recommended (see section 4.5 'Interactions with other medicines and other forms of interaction).

Paediatric population
A.VOGEL GINKGOFORCE® is not recommended for use in children under 12 years of age.
A.VOGEL GINKGOFORCE®, (due to its alcohol content) may impact sensitive individuals during daily activities such as learning ability, physical activities, or affect appetite or sleep patterns.

4.5 Interaction with other medicines and other forms of interaction
- Taken concomitantly with anticoagulants (e.g. phenprocoumon and warfarin) or antiplatelet medicines (e.g. clopidogrel, acetylsalicylic acid (aspirin) and other non-steroidal anti-inflammatory medicines), their effect may be influenced/increased.
- Available studies indicate that warfarin does not have an interaction with *Ginkgo biloba*, but adequate monitoring is advised when starting, when changing dose, or when ending A.VOGEL GINKGOFORCE® intake or if changing product.
- Caution is advised if combining A.VOGEL GINKGOFORCE® and dabigatran. A.VOGEL GINKGOFORCE® may inhibit P-glycoprotein at the intestinal level. This may give rise to increased exposure of medicines markedly affected by P-glycoprotein in the intestine such as dabigatran etexilate.
- 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 A.VOGEL GINKGOFORCE® and efavirenz is not recommended; plasma concentrations of efavirenz may be decreased because of CYP3A4 induction (see section 4.4 'Special warnings and precautions for use').

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/Contraception in males and females
No information available.

Pregnancy
A.VOGEL GINKGOFORCE® may impair the ability of platelets to aggregate. The tendency for bleeding may be increased. Animal studies with *Ginkgo biloba* are insufficient with respect to reproductive toxicity (see section 5.3 'Preclinical safety data').
The use of A.VOGEL GINKGOFORCE® during pregnancy is not recommended.

Lactation
It is unknown whether *Ginkgo biloba* metabolites are excreted in human milk. A risk to the new-borns / infants cannot be excluded.
In the absence of sufficient data, the use of A.VOGEL GINKGOFORCE® during breastfeeding is not recommended.

Fertility
No specific studies with A.VOGEL GINKGOFORCE® in humans have been conducted to evaluate effects on fertility. In a study with *Ginkgo biloba* in female mice, effects on fertility were seen (see section 5.3 'Preclinical safety data').

4.7 Effects on ability to drive and use machines
No adequate studies on the effect on the ability to drive and use machines have been performed.

It is not always possible to predict to what extent A.VOGEL GINKGOFORCE® may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which A.VOGEL GINKGOFORCE® affects them.

A.VOGEL GINKGOFORCE® contains alcohol.

4.8 Undesirable effects
Adverse reactions are grouped into the following frequency classifications: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be assessed from the available data)

Tabulated list of adverse reactions

Body System	Undesirable effect
Blood and lymphatic system disorders:	*Frequency not known:* Bleeding of individual organs (eye, nose, cerebral and gastrointestinal haemorrhage).
Nervous system disorders:	*Very common:* headache. *Common:* dizziness.
Gastrointestinal disorders:	*Common:* diarrhoea, abdominal pain, nausea, vomiting.
Immune system disorders:	*Frequency not known:* Hypersensitivity reactions (allergic shock).
Skin and subcutaneous tissue disorders:	*Frequency not known:* Allergic skin reactions (erythema, oedema, itching and rash).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
None known.
In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).
Treatment of overdosage should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
D33.6 Western Herbal Medicine
ATC code: N06DX02

The exact mechanism is not known.
Human pharmacological data show increased EEG vigilance in geriatric subjects, reduction in blood viscosity and improved cerebral perfusion in specific areas in healthy men (60 – 70 years) and reduction in platelet aggregation. Additionally, vasodilating effects on forearm blood vessels causing increase regional blood flow are shown (European Union herbal monograph on Ginkgo biloba L., folium; EMA/HMPC/321097/2012).

5.2 Pharmacokinetic properties
Following oral administration (as solution) of 120 mg of *Ginkgo biloba* extract, the mean absolute bioavailability has been shown in humans for the terpene lactones ginkgolide A (80 %), ginkgolide B (88 %) and bilobalide (79 %). Peak plasma concentrations of terpene lactones were in the range of 16 – 22 ng/ml for ginkgolide A, 8 – 10 ng/ml for ginkgolide B and 27 – 54 ng/ml of bilobalide when given as tablets. The corresponding half-lives of ginkgolide A, B and bilobalide were 3 – 4, 4 – 6 and 2 - 3 hours, respectively. 120 mg *Ginkgo biloba* extract, given as solution peak plasma concentrations, were 25 – 33 ng/ml, 9 – 17 ng/ml and 19 – 35 ng/ml for ginkgolide A, B and bilobalide, respectively. The related half-life for ginkgolide A was 5 hours, for ginkgolide B was 9 – 11 hours and for bilobalide 3 – 4 hours (European Union herbal monograph on *Ginkgo biloba* L., folium; EMA/HMPC/321097/2012).

5.3 Preclinical safety data
Chronic toxicity
Chronic toxicity was tested orally over 6 months in rats and dogs with daily dosages of 20 and 100 mg/kg BW (corresponding to safety factor of up to 3,3 in rats and 11,6 in dogs), as well as with incremental doses of 300, 400 and 500 mg/kg BW (rat) or 300 and 400 mg/kg BW (dog) (corresponding to a safety factor up to 16,8 in rats and 46,3 in dogs). The results showed only for dogs a low toxicity in the highest dosage group.

Reproductive toxicity
Only limited information is available in reproductive toxicity of the *Ginkgo biloba* dry extract. The published data are contradictory. While an older study in rats and rabbits and a newer study in mice revealed no teratogenic, embryotoxic or adverse reproductive effects, another study in mice showed effects on reproductive parameters, such as fertility and reproductive performance and it evoked vaginal bleeding. Also tests with unspecified or slightly different *Ginkgo biloba* extracts pointed towards effects on foetal development (with or without maternal toxicity) or caused subcutaneous bleeding, hypopigmentation, growth inhibition and anophthalmia in chicken embryos.
Adequate tests on reproductive toxicity do not exist.

Mutagenity, carcinogenity
Tests on genotoxicity and carcinogenicity are not available for the *Ginkgo biloba* dry extract.

An extract, similar to the EMA herbal monograph relevant extract, was tested in a series of studies for genotoxicity and carcinogenicity. It was positive for gene mutation in bacteria. A peripheral mouse erythrocytes micronucleus test provided a negative result in male and an equivocal result in female animals.

The thyroid gland tumours found in a rat carcinogenicity study and hepatocellular carcinoma found in a mouse carcinogenicity study are considered rodent specific, non-genotoxic response associated (with long-term treatment) with high doses of hepatic enzyme inducers.
These types of tumours are not considered relevant to humans. The extract did not induce measurable genotoxic effects in mice up to 2 000 mg/kg.

(European Union herbal monograph on *Ginkgo biloba* L., folium; EMA/HMPC/321097/2012).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Contains more than 60 % *v/v* alcohol.
Purified Water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months unopened.

6.4 Special precautions for storage
No special storage conditions.
Store at or below 25 °C.
Store in the original package/container.

6.5 Nature and contents of container
Packed in an amber type III glass bottle, with plastic dropper (LDPE) and screw cap (HDPE) with tamper evident seal.

Pack size: 30 ml, 50 ml and 100 ml.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION
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8 REGISTRATION NUMBER
29/34/0535

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13 May 1997

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