EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2014
EMA/HMPC/321097/2012
Committee on Herbal Medicinal Products (HMPC)

Community herbal monograph on *Ginkgo biloba* L., folium

Draft

Discussion in Working Party on Community monographs and Community list (MLWP)	May, Sep, Nov 2012 Jan, Mar, May, Jul, Sep, Nov 2013
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	28 January 2014
End of consultation (deadline for comments). Comments should be provided using this template to hmpc.secretariat@ema.europa.eu	15 June 2014
Rediscussion in Working Party on Community monographs and Community list (MLWP)	
Adoption by Committee on Herbal Medicinal Products (HMPC)	

Keywords	Herbal medicinal products; HMPC; Community herbal monographs; well-established medicinal use; traditional use; *Ginkgo biloba* L., folium; Ginkgo folium; Ginkgo leaf

BG (bulgarski): Гинко, лист CS (čeština): jinanový list DA (dansk): Ginkgoblad DE (Deutsch): Ginkgoblätter EL (elliniká): ΓΙΓΚΟΥ ΦΥΛΛΟ EN (English): Ginkgo leaf ES (español): Ginkgo, hoja de ET (eesti keel): hõlmikpuuleht FI (suomi): neidonhiuspuu, lehti FR (français): Ginkgo (feuille de) HR (hrvatski): ginkov list HU (magyar): Páfrányfenyőlevél IT (italiano): Ginkgo foglia	LT (lietuvių kalba): Ginkmedžių lapai LV (latviešu valoda): Ginka lapas MT (Malti): Werqa tal-Ginko NL (Nederlands): Ginkgo PL (polski): Liść miłorzębu japońskiego PT (português): Ginkgo, folha RO (română): frunză de ginkgo SK (slovenčina): List ginka SL (slovenščina): list ginka SV (svenska): Ginkgoblad *IS (íslenska)*: *NO (norsk):* Ginkgoblad

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Community herbal monograph on *Ginkgo biloba* L., folium

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[1]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended
Ginkgo biloba L., folium (Ginkgo leaf)	*Ginkgo biloba* L., folium (Ginkgo leaf)
i) Herbal substance	i) Herbal substance
Not applicable.	Not applicable.
ii) Herbal preparations	ii) Herbal preparations
Dry extract (DER 35-67:1), extraction solvent: acetone 60% m/m	Powdered herbal substance

3. Pharmaceutical form

Well-established use	Traditional use
Herbal preparations in solid or liquid dosage forms for oral use.	Herbal preparations in solid dosage forms for oral use.
The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia.	Traditional herbal medicinal product for the relief of heaviness of legs and the sensation of cold hands and feet associated with minor circulatory disorders, after serious conditions have been excluded by a medical doctor.

[1] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance

4.2. Posology and method of administration

Well-established use	Traditional use
Posology *Adults, elderly* Single dose: 120-240 mg Daily dose: 240 mg There is no relevant indication for children and adolescents. **Duration of use** Treatment should last for at least 8 weeks. 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. **Method of administration** Oral use.	**Posology** *Adults, elderly* Single dose: 250-360 mg Daily dose: 750 mg The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). **Duration of use** If the symptoms persist for more than 2 weeks, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use.

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance. Pregnancy (see section 4.6. 'Fertility, pregnancy and lactation').	Hypersensitivity to the active substance. Pregnancy (see section 4.6. 'Fertility, pregnancy and lactation').

4.4. Special warnings and precautions for use

Well-established use	Traditional use
If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted. 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 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 preparations –	The use in children and adolescents under 18 years of age has not been established due to lack of adequate data. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified healthcare professional should be consulted. The following special warnings are based on observations reported for extracts of *G. biloba*. 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.

Well-established use	Traditional use
cannot be excluded. Concomitant use of *G. biloba* containing products and efavirenz is not recommended (see section 4.5).	Preparations containing Ginkgo 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 preparations – cannot be excluded. Concomitant use of *G. biloba* containing products and efavirenz is not recommended (see section 4.5).

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
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 *G. biloba* products, but adequate monitoring is advised when starting, when changing *G. biloba* dose, when ending *G. biloba* intake or if changing product. An interaction study with talinolol indicates that *G. 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 *G. biloba* and dabigatran. One interaction study has indicated that the C_{max} of nifedipine may be increased by *G biloba*. In some individuals, increases by up to 100% were observed resulting in dizziness and increased severity of hot flushes. Concomitant use of *G. biloba* preparations and efavirenz is not recommended; plasma concentrations of efavirenz may be decreased because of induction of CYP3A4 (see also section 4.4).	For extracts of *G. biloba*, the following interactions have been reported. It cannot be excluded that they may occur with the powder. 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 *G. biloba* products, but adequate monitoring is advised when starting, when changing *G. biloba* dose, when ending *G. biloba* intake or if changing product. An interaction study with talinolol indicates that *G. 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 *G. biloba* and dabigatran. One interaction study has indicated that the C_{max} of nifedipine may be increased by *G biloba*. In some individuals, increases by up to 100% were observed resulting in dizziness and increased severity of hot flushes. Concomitant use of *G. biloba* preparations and efavirenz is not recommended; plasma concentrations of efavirenz may be decreased

Well-established use	Traditional use
	because of induction of CYP3A4 (see also section 4.4).

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
Pregnancy: *G. 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) **Lactation**: It is unknown whether *G. 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 *G. 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).	For extracts of *G. biloba*, the following effects have been reported. It cannot be excluded that they may occur with the powder. **Pregnancy**: *G. 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) **Lactation**: It is unknown whether *G. 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 *G. 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

Well-established use	Traditional use
No adequate studies on the effect on the ability to drive and use machines have been performed.	No adequate studies on the effect on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Well-established use	Traditional use
<u>Blood and lymphatic system disorders</u> Bleeding of individual organs have been reported	For extracts of *G. biloba*, the following undesirable effects have been reported. It cannot be excluded

Well-established use	Traditional use
(eye, nose, cerebral and gastrointestinal haemorrhage). The frequencies are not known. Nervous system disorders Very common: headache Common: dizziness Gastrointestinal disorders Common: diarrhoea, abdominal pain, nausea, vomiting Immune system disorders Hypersensitivity reactions (allergic shock) may occur. The frequencies are not known. Skin and subcutaneous tissue disorders Allergic skin reactions (erythema, oedema, itching and rash) may also occur. The frequencies are not known. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	that they may occur with the powder. Blood and lymphatic system disorders Bleeding of individual organs (eye, nose, cerebral and gastrointestinal haemorrhage) Nervous system disorders Headache and dizziness. Gastrointestinal disorders Diarrhoea, abdominal pain, nausea and vomiting. Immune system disorders Hypersensitivity reactions (allergic shock). Skin and subcutaneous tissue disorders Allergic skin reactions (erythema, oedema, itching and rash). If other adverse reactions not mentioned above occur, a doctor or a qualified healthcare professional should be consulted.

4.9. Overdose

Well-established use	Traditional use
No case of overdose has been reported.	No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: Other anti-dementia drugs 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 increased regional blood flow are shown.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
Following oral administration (as solution) of 120 mg of the Ginkgo 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 when given as tablets. The corresponding half-lives of ginkgolide A and B and bilobalide were 3-4, 4-6 and 2-3 hours, respectively. 120 mg *G. 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 ginkoglide B 9-11 hours and for bilobalide 3-4 hours.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.3. Preclinical safety data

Well-established use	Traditional use
Chronic toxicity: Chronic toxicity was tested orally over 6 months in rats and dogs with daily dosages of 20 and 100 mg/kg BW, as well as with incremental doses of 300, 400 and 500 mg/kg BW (rat) or 300 and 400 mg/kg BW (dog). The data revealed no evidence of any biochemical, haematological or histological damage. Hepatic and renal functions were not impaired. *Reproductive toxicity:* *G. biloba* has not been systematically evaluated for its capacity to cause teratogenic effects. Ginkgo extract administration to pregnant rats produced a decrease in fetal weight at maternal doses of 7 and 14 mg/kg/day in the absence of maternal toxicity. In female mice there was a dose-dependent ovarian toxic effect (significantly reduced ovarian follicle counts, reabsorption index, implantation index and fetal viability in 14.8 mg/kg/day dose of Ginkgo extract EGb 761). In the chicken embryo, an unspecified gingko	For extracts of *G. biloba*, the following non-clinical safety data have been concluded from reports on preparations of *G. biloba*. It cannot be excluded that they are also of relevance for the powder. *Chronic toxicity:* Chronic toxicity was tested orally over 6 months in rats and dogs with daily dosages of 20 and 100 mg/kg BW, as well as with incremental doses of 300, 400 and 500 mg/kg BW (rat) or 300 and 400 mg/kg BW (dog). The data revealed no evidence of any biochemical, haematological or histological damage. Hepatic and renal functions were not impaired. *Reproductive toxicity:* *G. biloba* has not been systematically evaluated for its capacity to cause teratogenic effects. Ginkgo extract administration to pregnant rats produced a decrease in fetal weight at maternal doses of 7 and 14 mg/kg/day in the absence of maternal toxicity. In female mice there was a dose-dependent ovarian toxic effect (significantly

Well-established use	Traditional use
extract dose-dependently caused subcutaneous bleeding, hypopigmentation, growth inhibition and anophthalmia. A *G. biloba* extract similar to the monograph relevant extract was tested in a series of studies for genotoxicity and carcinogenicity. It was positive for gene mutation in bacteria and equivocal and negative for chromosome mutations in two separate *in vivo* tests in peripheral erythrocytes and bone marrow cells in mouse. A carcinogenicity study was conducted on a *Ginkgo biloba* extract similar to the monograph relevant extract. 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. Overall, from the carcinogenicity study there is no proof for an increased cancer risk identified at present for patients taking Ginkgo medicinal products at their approved posology.	reduced ovarian follicle counts, reabsorption index, implantation index and fetal viability in 14.8 mg/kg/day dose of Ginkgo extract EGb 761). In the chicken embryo, an unspecified gingko extract dose-dependently caused subcutaneous bleeding, hypopigmentation, growth inhibition and anophthalmia. A *G. biloba* extract similar to the monograph relevant extract was tested in a series of studies for genotoxicity and carcinogenicity. It was positive for gene mutation in bacteria and equivocal and negative for chromosome mutations in two separate *in vivo* tests in peripheral erythrocytes and bone marrow cells in mouse. A carcinogenicity study was conducted on a *G. biloba* extract similar to the monograph relevant extract. 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. Overall, from the carcinogenicity study there is no proof for an increased cancer risk identified at present for patients taking Ginkgo medicinal products at their approved posology.

6. Pharmaceutical particulars

Well-established use	Traditional use
Not applicable.	Not applicable.

7. Date of compilation / last revision

28 January 2014