EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Ginkgo biloba* L., folium

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Ginkgo biloba* L., folium
Herbal preparation(s)	Dry extract (35-67:1) of *Ginkgo biloba* leaf is refined and quantified to 22-27% ginkgoflavonglycosides, represented by quercetin, kaempherol and isorhamnetin and 5-7% terpene lactones, represented by ginkgolides A, B, C (2.8-3.4%) and bilobalide (2.6-3.2%). The content of ginkgolic acids is less than 5 ppm. Extraction solvent: acetone 60%. Powdered herbal substance
Pharmaceutical form(s)	Herbal preparation in solid dosage forms for oral use.
Rapporteur	Dr Jacqueline Wiesner
Assessor(s)	Eva-Maria Eibl

Note: This draft assessment report is published to support the release for public consultation of the draft Community herbal monograph on *Ginkgo biloba* L., folium. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by interested parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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Table of contents

1. Introduction 4
1.2. Information about products on the market in the Member States 5
1.3. Search and assessment methodology 30

2. Historical data on medicinal use 30
2.1. Information on period of medicinal use in the Community 30
2.2. Information on traditional/current indications and specified substances/preparations 31
2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications 32

3. Non-Clinical Data 32
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 33
3.1.1. Primary pharmacodynamic 33
3.1.2. Secondary pharmacodynamic 34
3.1.3. Safety pharmacology 35
3.1.4. Pharmacodynamic interactions 37
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 37
3.2.1. Absorption 37
3.2.2. Distribution 37
3.2.3. Metabolism 37
3.2.4. Elimination 38
3.2.5. Pharmacokinetic interactions with other medicinal products 38
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof 39
3.3.1. Single dose toxicity 39
3.3.2. Repeated dose toxicity 40
3.3.3. Genotoxicity 40
3.3.4. Carcinogenicity 40
3.3.5. Reproductive and developmental toxicity 42
3.3.6. Local tolerance 45
3.3.7. Other special studies 45
3.4. Overall conclusions on non-clinical data 46

4. Clinical Data 48
4.1. Clinical Pharmacology 48
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 48
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 50
4.2. Clinical Efficacy 58
4.2.1. Dose response studies 58
4.2.2. Clinical studies (case studies and clinical trials) 58
4.2.3. Clinical studies in special populations (e.g. elderly and children) 107
4.3. Overall conclusions on clinical pharmacology and efficacy 109

5. Clinical Safety / Pharmacovigilance 111
5.1. Overview of toxicological/safety data from clinical trials in humans 111
5.2. Patient exposure 111
5.3. Adverse events and serious adverse events and deaths 111
5.4. Laboratory findings 118
5.5. Safety in special populations and situations 118
5.6. Overall conclusions on clinical safety 118
6. Overall conclusions 119
Annex 120
List of references 120

1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

There is a monograph on Ginkgo leaf published in the European Pharmacopoeia (Ph. Eur. 7th edition 2012 (7.5), ref. 01/2011:1828).

The herbal substance consists of the whole or fragmented, dried leaf of *Ginkgo biloba* L.

The leaf is greyish or yellowish-green or yellowish-brown. The upper surface is slightly darker than the lower surface. The petioles are about 4-9 cm long. The lamina is about 4-10 cm wide, fan-shaped, usually bilobate or sometimes undivided. Both surfaces are smooth, and the venation dichotomous, the veins appearing to radiate from the base; they are equally prominent on both surfaces. The distal margin is incised, irregularly and to different degrees, and irregularly lobate or emarginate. The lateral margins are entire and taper towards the base.

Synonyms: Fossil tree, Kew tree, Maidenhair Tree, Yin Xing (whole plant), Yin Xing Ye (leaves)

Constituents: **(Chan 2007, van Beek 2000)**

Terpenes

- Triterpenelactones (Diterpenes: ginkgolides A, B, C, J (0.06-0.23%) and sesquiterpene: bilobalide (up to 0.26%))
- Triterpenes (steroids, phytosterols)
- Carotenoids
- Polyprenols (Di-trans-poly-cis-octadecaprenol) concentration ranges from 0.04% to 2.0%
- Volatile terpenes

Flavonoids not less than 0.5%

- Flavanols (catechins)
- Flavones (Aglycones, monoglycosides and biflavones with a concentration of 0.4% to 1.9%)
- Flavonols (the aglycones isorhamnetin, kaempferol, quercetin and myricetin have a concentration of 0.2% to 1.4% w/w)

Organic acids

Polyacetate derived compounds

- Alkyl phenolic acids and alkyl phenols (ginkgolic acid, cardanols (approx. 0.1%))
- Long chain hydrocarbons (waxes)
- Lipids

Others (Carbohydrates, miscellaneous organic compounds, inorganic compounds)

- Herbal preparation(s)

1. *Ginkgo biloba* dry extract is a component part of the European Pharmacopoeia. Actually the following monograph exists:

- Ginkgo dry extract, refined and quantified (Ph. Eur. 7th edition 2012 (7.5), ref. 04/2008:1827)

  This extract contains several chemical constituents, among which the two main constituents "flavones glycosides" (total 22.0-27.0%), represented by quercetin, kaempherol and isorhamnetin and "terpene lactones" (total 5.0-7.0), represented by ginkgolides A, B, C (2.8-3.4%) and bilobalide (2.6-3.2%). The content of ginkgolic acids is limited with max. 5 ppm. The limit value of 5 ppm was chosen since it complies with the detection limit recordable by routine methods, thus allowing to assure to a maximum degree removal of these compounds from therapeutically used extracts.

2. Powdered herbal substance

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

  The monograph is established on Ginkgo folium and preparations thereof.

1.2. Information about products on the market in the Member States

Austria: Well-established use

1. Dry extract of *Ginkgo biloba* leaves (EGb 761); DER 35-67:1; quantified to 19.2 mg ginkgoflavonglycosides and 4.8 mg terpene lactones (ginkgolides, bilobalide); extraction solvent acetone
2. Dry extract of *Ginkgo biloba* leaves standardised to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
3. Dry extract of *Ginkgo biloba* leaves standardised to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
4. Dry extract of *Ginkgo biloba* leaves, not further specified
5. Dry extract of *Ginkgo biloba* leaves; DER 35-67:1; extraction solvent: acetone 60%
6. Dry extract of *Ginkgo biloba* leaves (EGb 761) standardised to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
7. Dry extract of *Ginkgo biloba* leaves (EGb 761) standardised to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
8. See 6.
9. Dry extract of *Ginkgo biloba* leaves (EGb 761) standardised to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
10. 1 coated tablet contains 20 mg dry extract of *Ginkgo biloba* leaves standardised to 4,8 mg ginkgoflavonglycosides

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 2000	film-coated tablets containing 80 mg extract	2-3 times daily The amount of tablets per day is not stated

2. 1993	film-coated tablets containing 40 mg extract	2 times daily 1 tablet; if required the dosage can be increased to 3 times daily 1 tablet
3. 1993	drops 1 ml solution contains 40 mg extract	2 times daily 1 ml; if required the dosage can be increased to 3 times daily 1 ml
4. 1999	film-coated tablets containing 50 mg dry extract	3 times daily 1 tablet; duration of treatment comply with the disease pattern; should last min. 6-8 weeks
5. 1999	oral solution 100 ml solution contain 1.33 g extract	2 times daily 1 teaspoon; duration of treatment comply with the disease pattern; should last 6-8 weeks
6. 1999	film-coated tablets containing 40 mg extract	3 times daily 1 tablet during 8-12 weeks initial treatment: 3 times daily 1 tablet for 8-12 weeks follow-up treatment: if required 2 times daily 1 tablet dementia syndrome: 3 times daily 1-2 tablets
7. 1999	drops 1 mg (appropriate to 18 drops) solution contains 40 mg extract	initial treatment: 3 times daily 1 ml for 8-12 weeks follow-up treatment: if required 2 times daily 1 ml dementia syndrome: 3 times daily 1-2 ml
8. 1989	film-coated tablets containing 40 mg extract	3 times daily 1 tablet during 8-12 weeks follow-up treatment: if required 2 times daily 1 tablet dementia syndrome: 3 times daily 1-2 tablets
9. 1989	drops 1 ml contains 40 mg extract	3 times daily 1 ml during 8-12 weeks
10. 1993	coated tablets containing 20 mg extract	2-3 times daily 1-2 coated tablets

Indications:

1. For the symptomatic treatment of brain-related impairment of mental performance, memory impairment, impaired concentration, depressive mood, dizziness, and headache
2. Decrease of the brain performance with lack of concentration and weakness of memory, cold hands and feet with numbness, prickle, and calf pain at walking
3. Frequently occurring vertigo and tinnitus (clarification by a doctor), hearing loss (clarification by a doctor)
4. Decrease of the brain performance (such as weakness of memory, anxiety, depressive mood, cold hands and feet
5. See 4.
6. Cerebral insufficient blood supply or rather brain disorder with symptoms of decreasing intellectual performance and vigilance such as dizziness, tinnitus, headache, sight disorder, weakness of memory, anxiety and depressive mood, dementia syndrome. Peripheral arterial circulatory disorders with preservative perfusion reserve (claudication intermittent). For supportive treatment of impaired hearing because of a cervical syndrome.
7. See 6.

8. Cerebral insufficient blood supply and malnutrition or rather brain disorders with the symptoms of decreasing intellectual performance and vigilance such as dizziness, headache, sight disorder, weakness of memory, anxiety and depressive mood.
9. See 8.
10. See 8.

Belgium: Well-established use

1. Dry extract; DER 35-45:1; extraction solvent: acetone 60%; containing 24% flavones glycosides and 6% terpene lactones (ginkgolides, bilobalide)
2. Dry extract; DER 35-67:1; extraction solvent: acetone 60%; containing 24% flavones glycosides and 6% terpene lactones (ginkgolides, bilobalide)
3. Dry extract; DER 35-67:1; extraction solvent: acetone 60%; containing 24% flavones glycosides and 6% terpene lactones (ginkgolides, bilobalide)

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
1. 1998	capsules, hard containing 60 mg extract	Adults (> 16 years) 1 capsule 2 times daily; max. 6 capsules per day; intake longer than 3 months: under medical supervision
2. a) 2000 b) 2006 (line extension)	film-coated tablets a) containing 40 mg extract b) containing 120 mg extract	a) 1 tablet 3 times daily; max. 9 tablets per day; no use in children below 12 years; min. period of treatment: 8 weeks; intake longer than 3 months: under medical supervision b) 1-2 tablets once daily, max 2 tablets per day
3. a) 2002 b) 2002	a) coated tablets containing 40 mg extract b) oral solution	a) Adults: 1-2 tablets 3 times daily Venous insufficiency: 1 tablet 3 times daily; max. 9 tablets per day b) Adults: 1-2 ml 3 times daily Venous insufficiency: 1 ml 3 times daily; max. 9 ml per day

Indications:

1. Symptomatic treatment of disturbance in the cerebral functions, after exclusion of all serious pathologies; (OTC)
2. To delay the pathological symptoms typical of mild to moderate Alzheimer-type dementia with its concomitant disturbances in memory and problems in concentrating. The primary target group includes patients with dementia syndrome as a consequence of degenerative dementia, vascular dementia and “mixed” (hybrid) forms. Before initiating the therapy, it should be excluded that the disorder is caused by a specific underlying disease that needs other specific treatment. (medical prescription)
3. To delay the pathological symptoms typical of mild to moderate Alzheimer-type dementia with its concomitant disturbances in memory and problems in concentrating. The primary target group includes patients with dementia syndrome as a consequence of degenerative dementia, vascular dementia and “mixed” (hybrid) forms. Before initiating the therapy, it should be

excluded that the disorder is caused by a specific underlying disease that needs other specific treatment. (medical prescription).

Used in case of subjective symptoms of venous insufficiency of the lower limbs, such as heavy legs, after exclusion of all serious pathologies (such as flebitis, thromboflebitis, thrombosis).

Czech Republic: Well-established use

1. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (m/m); (EGb 761) for specification see additional comments
2. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (m/m); (EGb 761) for specification see additional comments
3. See 1.
4. See 2.
5. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (V/V); for specification see additional comments
6. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (V/V); for specification see additional comments
7. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (V/V); for specification see additional comments
8. *Ginkgo biloba* dry extract standardised to 35-67:1; extraction solvent acetone 60% (V/V); for specification see additional comments

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
1. 1992	oral drops, solution 1 ml contains 40 mg extract	in mental capacity disturbances, peripheral vascular insufficiency, sensory disturbances: 1 ml 3 times daily; duration of use minimum 6-8 weeks in dementia: 1-2 ml 3 times daily; duration of use minimum 8 weeks
2. 1992	film-coated tablets containing 40 mg extract	in mental capacity disturbances, peripheral vascular insufficiency, sensory disturbances: 1 tablet 3 times daily; duration of use minimum 6-8 weeks dementia: 1-2 tablets 3 times daily; duration of use minimum 8 weeks
3. 1995	oral drops, solution 1 ml contains 40 mg extract	in dementia syndromes: 1-2 ml 3 times daily; duration of use minimum 8 weeks; after 3 months evaluation should be carried to determined, whether continuation of the treatment is eligible in peripheral obliterating arteriopathy, dizziness, tinnitus: 1 ml 3 times daily or 2 ml 2 times daily; duration of use minimum 6 weeks
4. 1995	film-coated tablets containing 40 mg extract	in dementia syndromes: 1-2 tablets 3 times daily; duration of use minimum 8 weeks; after 3 months evaluation should be carried to determined, whether continuation of the treatment is eligible in peripheral obliterating arteriopathy, dizziness, tinnitus:

		1 tablet 3 times daily or 2 tablets 2 times daily; duration of use minimum 6 weeks
5. 2002	oral drops, solution 1 ml contains 40 mg extract	in mild cerebrovascular insufficiency (dementia syndromes such as memory and concentration disturbances, emotional lability, dizziness, tinnitus, headaches): 1-2 ml 3 times daily in peripheral arterial occlusive disease: 1.5-2 ml 2 times daily in dizziness and tinnitus of vascular or involution character: 1.5-2 ml 2 times daily duration of use minimum 8 weeks, for improvement of gait in case of peripheral arterial occlusive disease minimum 6 weeks; after 3 month an evaluation should be carried to determined, whether continuation of the treatment is eligible
6. 2002	film-coated tablets contains 40 mg extract	in mild cerebrovascular insufficiency (dementia syndromes such as memory and concentration disturbances, emotional lability, dizziness, tinnitus, head aches): 1-2 tablets 3 times daily in peripheral arterial occlusive disease: 1.5-2 tablets 2 times daily in dizziness and tinnitus of vascular or involution character: 1.5-2 tablets 2 times daily duration of use minimum 8 weeks, for improvement of gait in case of peripheral arterial occlusive disease minimum 6 weeks; after 3 month an evaluation should be carried to determined, whether continuation of the treatment is eligible
7. 2006	film-coated tablets containing 80 mg extract	symptomatic treatment of cerebral insufficiency: 1 tablet 2-3 times daily in peripheral arterial occlusive disease, in dizziness and tinnitus of vascular or involution character: 1 tablet 2 times daily duration of use minimum 8 weeks, for improvement of gait in case of peripheral arterial occlusive disease minimum 6 weeks; after 3 month an evaluation should be carried to determined, whether continuation of the treatment is eligible
8. 2006	film-coated tablets containing 120 mg extract	symptomatic treatment of cerebral insufficiency: 1 tablet 1-2 times daily in peripheral arterial occlusive disease, in dizziness and tinnitus of vascular or involution character: 1 tablet 1 times daily duration of use minimum 8 weeks, for improvement of gait in case of peripheral arterial occlusive disease minimum 6 weeks; after 3 month an evaluation should be carried to determined, whether continuation of the treatment is eligible

For all products: In dizziness and tinnitus of vascular or involution character treatment longer than 6-8 weeks does not have any therapeutically benefit

Indications:

1. Syndrome of dementia (primary degenerative dementia of Alzheimer type, vascular dementia, mixed forms of dementia); for treatment of symptoms such as (loss of concentration; memory disturbances, emotional lability) in elderly, based on chronic cerebrovascular insufficiency; peripheral blood circulation and microcirculation disorders: peripheral arterial obstructive disease of hind limbs at stadium 1-II according to Fontaine (claudicatio intermittens), Raynaud syndrome, acroparesthaesia, enhanced capillary fragility, etc.; sensory disorders based on vascular insufficiency (vertigo, tinnitus, hearing impairment and vision impairment in elderly based on insufficient blood circulation in retina
2. See 2.
3. Syndrome of dementia (primary degenerative dementia of Alzheimer type, vascular dementia, mixed forms of dementia); brain function disorders such as memory and concentration disturbances, depression, dizziness, tinnitus, head aches due to organic dysfunction of CNS as a part of complex dementia therapy; peripheral obliterating arteriopathy at stadium II according to Fontaine scale; dizziness and tinnitus of vascular or involution character
4. See 3.
5. For symptomatic treatment of cerebral insufficiency such as memory and concentration disturbances, emotional lability, dizziness, tinnitus and head aches; mild to moderate dementia syndromes including primary degenerative dementia, vascular dementia and mixed forms; peripheral arterial occlusive disease (claudicatio intermittens); dizziness and tinnitus of vascular or involution character
6. See 5.
7. See 5.
8. See 5.

Risks:

1. *Contraindications:* hypersensitivity to the drug substance, bleeding dispositions*. Special warning:* Not to be used in pregnancy and lactation, and in children bellow 12 years, not intended for hypertension therapy. *Interactions:* caution is recommended in concomitant use with salicylates and barbiturates. *Undesirable effects:* in isolated cases gastrointestinal discomfort such as nausea, diarrhoea, very rare palpitation, hypotension, arrhythmia, retrosternal pain
2. See 1.
3. *Contraindications:* hypersensitivity to the drug substance, bleeding dispositions. *Special warning:* Not to be used in pregnancy and lactation, and in children bellow 12 years, not intended for hypertension therapy. Caution is recommended in case of concomitant use of medicinal products with similar effect (vasodilatants, medicinal products causing tachycardia etc.). *Undesirable effects:* in isolated cases gastrointestinal discomfort, headaches, congestion, allergic skin reactions, very rare haemorrhage
4. See 3.
5. *Contraindications:* hypersensitivity to the drug substance. *Special warning:* Not to be used in children bellow 12 years, not recommended in haemorrhage, caution is recommended in case of concomitant use of medicinal products with similar effect (vasodilatants, antiarrythmics).

Interactions: caution is recommended in concomitant use with salicylates and barbiturates. *Pregnancy and lactation:* No experience with use in humans, benefit/risk evaluation is needed. *Undesirable effects:* very rare gastrointestinal discomfort, headaches, congestions, allergic skin reactions. In isolated cases during long term use haemorrhage; one case of subdural haematoma when 120 mg/day of ginkgo extract had been used for 2 years has been reported

6. See 5.

7. *Contraindications:* hypersensitivity to the drug substance. Special warning: Not to be used in children bellow 12 years. *Pregnancy and lactation:* No experience with use in humans, benefit/risk evaluation is needed. *Interactions:* in case of long term use concomitant medication with medicinal products affecting clotting should be avoided. *Undesirable effects:* very rare gastrointestinal discomfort, headaches, allergic skin reactions, in isolated cases during long term use haemorrhage

8. See 7.

Combination products:

Average number of combination substances: 2-3. The main combination substances are ginkgo dry extract and ginseng dry extract.

Additional comments:

Preparations 1. – 4.

Ginkgo biloba dry extract standardised to 35-67:1; extraction solvent acetone 60% m/m; (EGb 761); specification:

Test	**Release specification**	**Stability specification**
Assays		
-Ginkgoflavonglycosides (HPLC)	22.0–26.4 g/100 g (DAB+Ph.Eur. 22.0–27.0 %)	22.0–26.4 g/100 g 95.0–105.0% of initial value
- Terpene lactones (HPLC)	5.4–6.6 g/100 g (DAB 5.0–7.0 %)	5.4–6.6 g/100 g 90.0–110.0% of initial value
Ginkgolides A,B,C	2.8–3.4 g/100 g (~Ph.Eur+DAB)	2.8–3.4 g/100 g
Bilobalide	2.6–3.2 g/100 g (~Ph.Eur+DAB)	2.6–3.2 g/100 g
Proanthocyanidins (photometry)	NMT 9.5 %	-
Biflavones (HPLC)	NMT 0.1 %	-
Ginkgolic acids (HPLC)	NMT 5.0 ppm	-

Preparations 5) – 8)

Ginkgo biloba dry extract standardised to 35-67:1; extraction solvent acetone 60% (V/V); specification

Test	**Limit**
Ginkgolic acids as anacardic acid – HPLC	NMT 5.0 ppm
Assays - Ginkgoflavonglycosides–HPLC - Terpenes–GC Ginkgolides A,B,C,J and bilobalide - Ginkgolides A, B and C	 NLT 24.0–29.0 % NLT 6.0–9.0 % 2.6–3.2 %

During second half of the year (2008) specification will be adapted in accordance with the Ph.Eur. monograph 04/2008:1827

Denmark: Well-established use

1. Dry extract, refined, of *Ginkgo biloba* L., folium (ginkgo leaf) corresponding to 9.6 mg ginkgoflavonglycosides and 2.4 mg terpene lactones; first extraction solvent: acetone/water 60/40% (w/w)
2. Dry extract, refined, of *Ginkgo biloba* L., folium (ginkgo leaf) corresponding to 24 mg ginkgoflavonglycosides and 6 mg terpene lactones; first extraction solvent: acetone 60-65%
3. Extract of *Ginkgo biloba* leaf (*Ginkgo biloba* L., folium rec.) corresponding to 14.4 mg ginkgoflavonglycosides and 3.6 mg terpene lactones; extraction solvent: acetone 50-90% (V/V)
4. Product with brandname
5. Product with brandname

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
1. marketed around 1990, MA in 1995	film-coated tablets containing 40 mg extract	1 tablet 3-4 times daily; not to be used in children below 12 years due to lack of experience
2. marketed around 1990, MA in 1996	film-coated tablets containing 100 mg extract	1-2 tablets daily
3. 2005	film-coated tablets content is not indicated	1 tablet daily
4. 1995	film-coated tablets content is not indicated	not indicated
5. 1997	film-coated tablets containing 40 mg extract	1 tablet three times daily

Indications:

1. Herbal medicinal product in long-term symptoms as memory problems, concentration problems, tiredness, dizziness (vertigo) and tinnitus in elderly people, where a doctor has excluded other underlying disease; herbal medicinal product in trends to cold hands and feet and in walking initiated pains in the legs, due to poor blood circulation
2. See 1.
3. Not indicated
4. Not indicated
5. See 1.

Risks:

1. Products with ginkgo leaf should not be used in the weeks up to a planned surgery; patients that experience spontaneous bleeding during treatment with ginkgo leaf should stop the treatment and contact a doctor; caution in epileptics, ginkgo leaf may decrease the effect of antiepileptic drugs or increase the vulnerability of seizures

The following text is from the SPC in DK:

Interactions with other medicinal products and other interactions:

Antiepileptika: As stated in the chapter ”contraindiations” in the SPC of DK: Sensitivity for ginkgo leaves or one of the auxiliary agents

Orale antikoagulantia: Might increase the effect of oral anticoagulant

NSAID: Possible increased risk of bleedings in NSAID including acetylsalicylic acid.

Calcium antagonists: Concomitant intake of ginkgo leaf and nifedipine has caused an increased heart frequency of 5-10% in well beings. The mechanism is not clear. Ginkgo leaf does not affect the pharmacokinetic of nifedipine in concomitant intake in well volunteers. The combination can be used.

Proton pump inhibitors: Ginkgo leaf (multiple doses) decrease AUC for a single dose omeprazole with 25-40% and increase clearance for omeprazole from 30-45% due to an induction of omeprazole's metabolism in CYP2C19. The interaction is not seen as clinical important. The combination can be used.

Anti-diabetics, sulfonamides: Ginkgo leaf (multiple doses) decreases AUC for a single dose tolbutamide with around 15%. The mechanism is not clear. The combination can be used.

The effect of concomitant intake of other medicinal products included medicine bought in other countries and other herbal medicinal products is not known.

Side effects:

1. seldom: increased tendency to bleeding*, headache, nausea, gastrointestinal disturbances

   very seldom: dizziness (vertigo), allergic skin reactions like rash and itching

   *Bleeding has been noted in a single case after long-term treatment with ginkgo leaves. Clinical sudies with standardised extracts have not shown any effect on coagulation.

2. See 1.

Additional comments:

We have for the time being 15 products with extract of GB with a MA. The rest are similar to the above mentioned products, since several companies have identical versions of their products, sold with other names. But the listed are the different extract forms as far I can see. We also have had other products with a MA or applied for an MA, but they are either withdrawn or did not receive an MA.

Estonia: Well-established use

1. Dry extract from ginkgo leaf, corresponding to 9.6 mg of flavones glycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide)
2. Dry extract from ginkgo leaf, corresponding to 14.4 mg of flavones glycosides and 3.6 mg terpene lactones (ginkgolides, bilobalide)
3. Dry extract from ginkgo leaf, corresponding to 24 mg of flavones glycosides and 6 mg terpene lactones (ginkgolides, bilobalide)
4. Dry extract from ginkgo leaf; extraction solvent: ethanol 60% (V/V); DER 1:4,5
5. Dry extract from ginkgo leaf, corresponding to 17.6-21.6 mg of flavones glycosides and 4.0-5.6 mg terpene lactones (ginkgolides, bilobalide); extraction solvent: acetone 60% (m/m); 1 tablet contains less than 0.4 µg ginkgolic acids; DER 35-67:1

6. Dry extract from ginkgo leaf, corresponding to 26.4-32.4 mg of flavones glycosides and 6.0-8.4 mg terpene lactones (ginkgolides, bilobalide); extraction solvent: acetone 60% (V/V); 1 tablet contains less than 0.6 µg ginkgolic acids; DER 35-67:1

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
1. 1998	tablets containing 40 mg extract oral solution 1 ml contains 40 g extract	oral; adults take 1 tablet 3 times daily oral; adults take 1 ml 3 times daily
2. 1999	film-coated tablets containing 60 mg extract	oral; adults take 1 tablet 2 times daily
3. 2000	film-coated tablets containing 100 mg extract	oral; adults take 1-2 tablets daily
4.2000	oral drops, solution 1 ml contains 910 mg extract	oral; adults take 10-20 drops 3 times daily
5. 2004	coated tablets containing 80 mg extract	oral; adults take 1 tablet 3 times daily
6. 2004	coated tablets containing 120 mg extract	oral; adults take 1 tablet 2 times daily

Indications:

For all products: Disorders in cerebral function (i.e. decline in memory and intellectual capacity, indisposition and anxiety). Circulatory functional disorders of extremities.

Risks:

For all products: Gastrointestinal upset, nausea, vomiting, diarrhoea, dry mouth, headache, dizziness, restlessness, sleep disturbance, skin rash

Combination products:

Average number of combination substances: 2-3. There are two combination products (capsule, gel). The main combination substances are troxerutin and heptaminol. One capsule contains 14 mg of extract (as dry extract) from ginkgo leaf (24% of flavones glycosides and 6% terpene lactones (ginkgolides, bilobalide)). 1 g of gel contains 30 mg of troxerutin and 1.4 mg of extract (as dry extract) from ginkgo leaf (24% of flavones glycosides and 6% terpene lactones (ginkgolides, bilobalide)).

France:

One product (ginkgo powder 180 mg) has been on the market as food supplement.

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
1984	Hard capsule	From 1984-2000: 360 mg (180x2) 3 times daily From 2000: 250 mg 3 times daily

The product is marketed for vertigo, improvement of blood circulation, heavy legs, haemorrhoids, memory deficit.

Germany: Well-established use

All preparations MA to date are from dry extract of *Ginkgo biloba* leaves. They comply with the monograph of Commission E (BAnz Nr. 133 vom 19.07.1994). Dry extract (DER 35-67:1) from *Ginkgo biloba* leaf is refined and quantified to 22-27% ginkgoflavonglycosides, represented by quercetin, kaempherol and isorhamnetin and 5-7% terpene lactones, represented by ginkgolides A, B, C (2.8-3.4%) and bilobalide (2.6-3.2%). The content of ginkgolic acids is less than 5 ppm.

Preparations in the following strengths are available:

30 mg/tablet: No. 1

40 mg/tablet or rather 40 mg/ml: No. 2-20, 23, 25-41, 46-50, 55-58, 63-72, 99-100, 103, 108-109

50 mg/tablet: No. 21-22, 24

60 mg/tablet: No. 92-93, 107

80 mg/tablet: No. 42-45, 59-62, 77, 80, 82-84, 88, 101-102, 110

120 mg/tablet: No. 51-54, 73-76, 78-79, 81, 85-87, 89-91, 94-98, 111-114

240 mg/tablet: No. 104-106, 115-117

Since when are the preparations on the market?

No. 2 since 1986; No. 3-4 since 1991; No. 31-34 since 1992; No. 5-7since 1994; No. 8-12, 15, 20-30, 35-45, 51-54 since 1995; No. 13-14, 16-19 since 1996; No. 57-63, 65, 67-68, 70-77, 82-89 since 1999; No. 46-50, 55-56, 64, 66, 69 since 2000; No. 78-79, 81 since 2001; No. 80, 90-93 since 2002; No. 94-98 since 2003; No. 1 since 2004; No. 99-102 since 2005; No. 103 since 2006; No. 104-108 since 2007; No. 109 since 2008; No. 110-111 since 2009; No. 112-114 since 2010; No. 115-117 since 2011

Pharmaceutical forms:

Film-coated tablets: No. 1-4, 9, 11, 21-22, 24-28, 31-38, 42-54, 59-63, 65, 67, 69, 71-76, 78-108, 110-117

Oral drops, solution: No. 5-8, 16, 17, 30, 41, 68

Oral liquid: No. 10, 12, 14-15, 20, 23, 29, 39-40, 55-58, 64, 66, 70, 109

Capsule, hard: No. 13, 18-19

Effervescent tablet: No. 77

Posology/daily dosage:

Dementia syndrome, peripheral arterial occlusive disease, vertigo, as an adjuvant in tinnitus

2 tablets 2 times daily (=120 mg): No. 1

1-2 tablets 2-3 times daily (=80-240 mg): No. 26-28

1 tablet 2 times daily (=120-240 mg): No. 92-93

Dementia syndrome

1-2 tablets 3 times daily (=120-240 mg): No. 2-4, 9, 25, 31-38, 46-50, 63, 65, 67, 69, 71-72, 99-100, 103, 108

20-40 drops (1-2 ml) 3 times daily (=120-240 mg): No. 5-8, 23, 29-30, 39-41

18-36 drops (1-2 ml) 3 times daily (=120-240 mg): No. 10, 55-58, 64, 66, 68, 70, 109

2-4 pumps (1-2 ml) 3 times daily (=120-240 mg): No. 14

20-40 drops (1-2 ml) 2-3 times daily (=80-240 mg): No. 15

1 tablet 3 times daily or 2 tablets 2 times daily (=120-200 mg): No. 21-22, 24

1 tablet 2-3 times daily (=160-240 mg): No. 42-45, 59-62, 77, 80, 82-84, 88, 101-102, 107, 110

1 tablet 2 times daily (=120-240 mg): No. 51-54, 79, 81, 112-114

1 tablet 1-2 times daily (=120-240 mg): No. 73-76, 85-87, 89

0.5-1 tablet 2 times daily (=120-240 mg): No. 78, 90-91, 94-98, 111

0.5 tablet 2 times daily (=240 mg): No. 104-106, 115-117

For the symptomatic treatment of brain-related impairment of mental performance

1-2 tablets 3 times daily (=120-240 mg): No. 11

17-34 drops (1-2 ml) 3 times daily (=120-240 mg): No. 12

1-2 capsules 3 times daily (=120-240 mg): No. 13, 18-19

25-50 drops (1-2 ml) 3 times daily (=120-240 mg): No. 16-17, 20

Peripheral arterial occlusive disease, vertigo, as an adjuvant in tinnitus

1.5-2 tablets 2 times daily (=120-160 mg): No. 9, 46-50, 63, 65, 67, 69, 103, 108

25 drops (1,25 ml) 3 times daily or rather 40 drops (2 ml) 2 times daily (=150-160 mg): No. 6

20-25 drops (1-1.25 ml) 3 times daily or rather 30-40 drops (1.5-2 ml) 2 times daily (=120-160 mg): No. 5, 7, 40

20 drops (1 ml) 3 times daily or rather 40 drops (2 ml) 2 times daily (=120-160 mg): No. 8, 23, 29-30, 39, 41

27-36 drops (1.5-2 ml) 2 times daily (=120-160 mg): No. 10, 55-58, 64, 66, 68, 70, 109

2 pumps (1 ml) 3 times daily or rather 4 pumps (2 ml) 2 times daily (=120-160 mg): No. 14

20 drops (1 ml) 3 times daily or rather 40 drops (2 ml) 2 times daily (=120-160 mg): No. 15

1 tablet 3 times daily or 2 tablets 2 times daily (=120-200 mg): No. 31-38, 71-72, 99-100

1 tablet 3 times daily (=150 mg): No. 21-22, 24

1 tablet 2 times daily (=120-240 mg): No. 42-45, 59-62, 77, 80, 82-84, 88, 101-102, 110

1 tablet 1-2 times daily (=120-240 mg): No. 51, 53-54, 79, 111-114

1 tablet 1 time daily (=120 mg): No. 73-76, 85-87, 89

For increasing the pain-free walking distance in patients with arterial occlusive disease, vertigo and tinnitus of vascular and involutive origin

1.5-2 tablets 2 times daily (=120-160 mg): No. 11

26-34 drops (1.5-2 ml) 2 times daily (=120-160 mg): No. 12

For increasing the pain-free walking distance in patients with arterial occlusive disease, vertigo and tinnitus

1 capsule 3 times daily or rather 2 capsules 2 times daily (=120-160 mg): No. 13, 18, 19

25 drops (1 ml) 3 times daily or rather 50 drops (2 ml) 2 times daily (=120-160 mg): No. 16-17, 20

1 tablet 3 times daily or 2 tablets 2 times daily (=120-200 mg): No. 25

Route of administration:

For taking the medicinal product 3 times daily it should be consumed in the morning, in the afternoon and in the evening, for a daily use of 2 times it should be taken in the morning and in the afternoon.

For film-coated tablets and hard capsules

Do not take the film-coated tablets or the hard capsules in a supine position. The tablet/capsule is swallowed whole (not chewed) with some liquid, preferably a glass of drinking water. It can be taken with or without a meal.

For oral drops and oral liquids

The drops are taken undiluted or in some water and afterwards washed down sufficient liquid, preferably a glass of drinking water. The drops can be taken with or without a meal.

For effervescent tablet

The effervescent tablets are dissolved by stirring in a glass of drinking water, about 200 ml. The tablets can be taken with or without a meal.

Duration of use:

Dementia syndrome

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.

Peripheral arterial occlusive disease

A treatment period of at least 6 weeks is required for improving performance with regard to walking distance.

Vertigo

No therapeutic benefit is gained by extending use beyond a 6 to 8-week period.

Tinnitus

Adjuvant therapy should be administered over a period of at least 12 weeks. If treatment is unsuccessful after 6 months, success can no longer be expected even after prolonged treatment.

Indications:

a) For the symptomatic treatment of brain-related impairment of mental performance, as part of an overall therapeutic strategy in dementia syndromes with the following main symptoms: memory impairment, impaired concentration, depressive mood, dizziness, tinnitus, headache.

b) For increasing the pain-free walking distance in patients with arterial occlusive disease of the legs (Fontaine Stage II intermittent claudication), as part of physiotherapy, including gait training.

c) Vertigo of vascular and involutive origin.

d) Adjuvant therapy in tinnitus of vascular and involutive origin.

e) Vertigo and tinnitus of vascular and involutive origin.

f) Adjuvant therapy in tinnitus.

a-d: No. 1, 4, 8, 29-32, 35-36, 38, 45-46, 48, 51, 53-54, 65, 67, 72, 93, 103, 108-114

a, b, e: No. 2, 5, 7, 9-14, 16-21, 25, 33-34, 37, 39-44, 47, 49-50, 55-64, 66, 68-71, 77, 82-89

a: No. 3, 52, 73-76, 78-79, 81, 90-91, 94-98, 104-107, 115-117

a, b: No. 6

a-c, f: No. 15, 22-24, 26-28, 80, 92, 99-102

Risks:

Contraindications:

Hypersensitivity to *Ginkgo biloba* extracts or to any other component of the medicinal product.
Pregnancy.

Special warnings and precautions for use:

There are no adequate studies on the use of medicinal products containing *Ginkgo biloba* in children and adolescents. It must therefore not be used in children below 12 years: No. 11-13, 15-18, 20-28, 46, 48, 78, 90-91, 94-97, 99-102, 108-110. All other products must be used in adults aged 18 or over.

In abnormal increased tendency to bleed (haemorrhagic diathesis) and concomitantly treatment with anticoagulants the medicinal product only should be taken after consulting a doctor.

As there is evidence to suggest that preparations containing *Ginkgo biloba* might increase susceptibility to bleeding, these medicinal products must be discontinued as a precaution prior to surgery.

In patients with epilepsy, onset of further seizures - promoted by intake of ginkgo preparations - cannot be excluded. It has been argued that this might be associated with the 4'-O-methylpyridoxine content.

Interactions:

If a preparation containing *Ginkgo biloba* is taken concomitantly with anticoagulants (e.g. phenprocoumon, warfarin, clopidogrel, acetylsalicylic acid and other non-steroidal anti-inflammatory drugs), their effect may be potentiated.

As with any medicinal product, it cannot be ruled out that any preparation containing *Ginkgo biloba* may influence the metabolism via cytochrome P450 3A4, 1A2 and 2C19 of various other medications, which could affect the potency and/or duration of action of the medications concerned. No adequate studies are available on this matter.

Pregnancy and lactation:

There is isolated evidence which suggest that preparations containing *Ginkgo biloba* can increase susceptibility to bleeding. Therefore preparations containing *Ginkgo biloba* must not be used during pregnancy (see section Contraindications).

There are no adequate studies on the use of medicinal products containing *Ginkgo biloba* during lactation. Therefore preparations containing *Ginkgo biloba* must not be used during lactation. It is not known whether the ingredients of the extract pass into breast milk.

Undesirable effects:

It is not possible to give any definite data on the frequency of undesirable effects reported with the intake of preparations containing *Ginkgo biloba*, as such undesirable effects have emerged via individual reports by patients, doctors or pharmacists. According to these reports, the following undesirable effects might occur in patients taking this medicine:

Bleeding of individual organs may occur, particularly with concomitant intake of anticoagulants, e.g. phenprocoumon, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (see also section Interactions).

Allergic shock may occur in hypersensitive individuals; allergic skin reactions (erythema, swelling of the skin, itching) may also occur.

Mild gastrointestinal complaints

Headache, dizziness or aggravation of pre-existing symptoms of dizziness may occur.

The herbal substance is not on the market.

Norway: Well-established use

1. *Ginkgo biloba* leaf dry extract (35-67:1); first extraction solvent: Acetone 60%
2. *Ginkgo biloba* leaf dry extract (3-4:1); first extraction solvent: Acetone 60-65%

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 1998	Capsule, hard containing 62.5 mg dry extract	1-2 tablets
2. 1996	Film-coated tablet containing 100 mg dry extract	1-2 tablets

Indications:

Used to improve blood circulation in for example cold hands and feet

Poland: Well-established use

1. *Ginkgo biloba* leaf dry extract, refined (35-67:1), containing 22.0-27.0% of flavonoids expressed as flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; first extraction solvent: Acetone 60% (m/m)

Since when on the market?	pharmaceutical form	Posology / daily dosage
1993	Capsule, hard	Oral use; adults: 120 mg in the morning and 120 mg in the evening; duration of use in patients with age linked impairment of memory and intellectual ability and patients with cerebral circulation disorders: First

		signs of improvement are usually observed after 3 weeks of treatment; it is possible to prolong the treatment up to 3 months; duration of use in patients with unspecific peripheral vascular disorders: Effects appear after many weeks of treatment (10-12 weeks according to reults of clinical trials)

Indications:

In age linked impairment of memory and intellectual capability; adjunctively in cerebral circulation disorders with manifestations like vertigo and tinnitus; adjunctively in patients suffering from unspecific peripheral vascular disorders with symptoms of intermittent claudication who practice exercises

Risks:

Adverse drug reaction:

Gastrointestinal complaints (nausea, constipation, diarrhoea), headache, bleeding, hypersensitivity reactions (pruritus, erythema)

Interactions:

Concomitant use with anticoagulant or antiplatelet medicines increases risks of bleeding; use with caution in patients simultaneously treated with inhibitors of proton pump, trazodone, nifedipine, thiazides

Warnings:

Patients with coagulation disorders should not use this drug without medical supervision; the treatment must be stopped 36 hours before surgical or dental operation

The herbal substance is on the market.

Poland: Traditional use

1. *Ginkgo biloba* leaf dry extract, refined (39.6-49.5:1), containing 22.0-27.0% of flavonoids expressed as flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Ethanol 50% (V/V)

Since when on the market?	**pharmaceutical form**	**Posology / daily dosage**
Before 1980	Capsule, hard	Oral use; adults: 80-160 mg 2 times daily with meals

Indications:

In mild disorders of peripheral circulation with feeling of cold hands and legs; adjunctively in mild age-linked impairment of intellectual capability

Risks:

Adverse drug reaction:

Gastrointestinal complaints (nausea, constipation, diarrhoea), headache, sleep disorders, palpitation, vertigo anxiety, hypersensitivity reactions (pruritus, erythema), bleeding

Interactions:

Concomitant use with anticoagulants, antiplatelet medicines, tipranavir, herbal drugs containing Allium sativum or Panax ginseng increases risks of bleeding; use with caution in patients simultaneously treated with inhibitors of proton pump (decreased efficacy of IIPs), trazodone (risk of increased adverse drug reaction of nifedipine), thiazides (risk of increased blood pressure)

Warnings:

Patients with coagulation disorders should not use this drug without medical supervision; the treatment must be stopped 36 hours before surgical or dental operation

The herbal substance is on the market.

Additional comments:

Other herbal medicinal products than well-established use and traditional herbal medicinal products:

1. *Ginkgo biloba* leaf dry extract (35-67:1) containing 24-29% of flavone glycosides, 6-9% of trepene lactones, 2.6-3.2% of bilobalide; extraction solvent: Acetone 60% (V/V)
2. *Ginkgo biloba* leaf dry extract (35-67:1) containing 22-26.4% flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Acetone 60% (m/m)
3. *Ginkgo biloba* leaf dry extract (35-67:1) corresponding to 8.8-10.8 mg of flavone glycosides, 1.12-1.3 mg of ginkgolides, 1.04-1.28 mg of bilobalide; extraction solvent: Aceton 60% (m/m)
4. *Ginkgo biloba* leaf dry extract containing 21.6-26.4% of flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Acetone 60% (m/m)
5. *Ginkgo biloba* leaf dry extract (35-67:1) containing 22-27% of ginkgoflavonglycosides, 5-7% of terpene lactones including 2.8-3.4% of ginkgolides A, B, C and 2.6-3.2% of bilobalide; extraction solvent: Acetone 60% (m/m)
6. *Ginkgo biloba* leaf dry extract (40ß-50:1) containing 24-27% flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Acetone 60 % (V/V)
7. *Ginkgo biloba* leaf dry extract (35-67:1) corresponding to 19.2-23.2 mg of flavone glycosides and 4.8-7.2 mg of terpene lactones (ginkgolides, bilobalide); extraction solvent: Acetone 60% (V/V)
8. *Ginkgo biloba* leaf dry extract (45-55:1) containing not less than 6 mg of ginkgoflavoneglycosides and 2-2.8 mg terpene lactones; extraction solvent: Ethanol 70% (V/V)
9. *Ginkgo biloba* leaf tincture (1:5); extraction solvent: Ethanol 60% (V/V)
10. *Ginkgo biloba* leaf tincture (1:5); extraction solvent: Ethanol 70% (V/V)

Since when on the market?	Pharmaceutical form	Posology/daily dosage
1. 1993	Capsule, hard containing 40 mg extract	Oral use; adults: 1 capsule 3 times daily; Duration of use: First signs of improvement are usually observed after 1 month of treatment. In order to fix therapeutic effects, especially in geriatric patiens, 3-month use is recommended
2. 1993	Film-coated tablet Containing 40 mg extract	Oral use; adults: 1-2 film-coated tablets 3 times daily
3. 1996	Film-coated tablet containing 40 mg extract	Oral use; adults: indication (a) 2 tablets 2-3 times daily, indication (b) 2 tablets 2 times daily; duration of use: 8-12 weeks, usually first signs of

Since when on the market?	Pharmaceutical form	Posology/daily dosage
		improvement are observed after 4-week treatment, use of 1 tablet 2 times daily as a maintenance treatment is recommended
4. 1999	Film-coated tablet containing 40 mg extract	Oral use; adults: 1 tablet 3 times daily
5. 2001	Film-coated tablet containing 80 mg extract	Oral use; adults: indication (a) 1 tablet 2-3 times daily, indication (b) 1 tablet 2 times daily; duration of use: 8-12 weeks, first signs of improvement are observed usually after 4-week treatment, use of 1 tablet 2 times daily as a maintenance treatment is recommended
6. 2002	Film-coated tablet containing 40 mg extract	Oral use; adults: 1 tablet 3 times daily; duration of use: 8-12 weeks
7. 2004	Capsule, hard containing 80 mg extract	Oral use; adults: indication (a) 1 capsule 2-3 times daily, indication (b) and (c) 1 capsule in the morning and 1 capsule in the evening
8. 2004	Film-coated tablet containing 40 mg extract	Oral use; adults: 1 tablet 3 times daily; duration of use: up to 10 weeks
9. 1997	Oral liquid	Oral use; adults and elderly: 5-10 ml 3 times daily
10. 1992	Oral liquid	Oral use; adults and elderly: 5-10 ml 3 times daily

Indications:

1. In cerebral circulation disorders with such symptoms as: impairment of memory and intellectual capability, vertigo and tinnitus. Adjunctively in disorders of peripheral circulation with pain during walking or feeling of cold hands and legs.
2. As symptomatic treatment in first signs of cognitive disorders caused by impaired cerebral circulation (memory and concentration disorders); in microcirculation disorders (vertigo and tinnitus); adjunctively for treatment of symptoms of peripheral circulation disorders (contractions, feeling of cold legs)
3. (a) In cerebral circulation disorders with such symptoms as weakened concentration, memory impairment, headache and vertigo, tinnitus, impaired sight and hearing

   (b) In disorders of peripheral circulation with accompanying feeling of cold legs or pain
4. (a) In elderly patients manifesting impaired cognitive and neurosensorial functions (except for Alzheimer's disease and other states of profound dementia). In cerebral circulation disorders with such symptoms as vertigo and tinnitus, impaired sight and hearing

   (b) Adjunctively for treatment of symptoms of peripheral circulation disorders – intermittent claudication in chronic peripheral obliterative arterial disease (stage 2)

   (c) Adjunctively for treatment of Raynaud's disease symptoms
5. See 3.
6. In cerebral circulation disorders with such symptoms as: impairment of memory and intellectual capability, headache and vertigo, tinnitus. Adjunctively in disorders of peripheral circulation (intermittent claudication, pains in legs, acanthaesthesia)
7. (a) In age-linked impairment of memory and intellectual capability

(b) Adjunctively in cerebral circulation disorders with manifestations like vertigo and tinnitus

(c) Adjunctively in disorders of peripheral circulation with pain during walking or feeling of cold hands and legs

8. Adjunctively in cerebral circulation disorders with such symptoms as vertigo and tinnitus; adjunctively in disorders of peripheral circulation (feeling of cold hands and legs, dysaesthesia, acanthaesthesia)
9. In disorders of peripheral circulation ; adjunctively in cerebral circulation disorders
10. In peripheral circulation disorders

Risks (adverse drug effects, lliteratrue):

Adverse drug reactions:

1. Very rarely gastrointestinal complaints (nausea, constipation, diarrhoea), headache, hypersensitivity reactions (pruritus, erythema)
2. Bleeding, mild gastrointestinal complaints, headache, vertigo, allergic skin lesions
3. See 1.
4. Gastrointestinal complaints, headache, skin lesions
5. See 1.
6. Very rarely skin lesions (pruritus, erythema), gastrointestinal complaints, headache
7. See 1.
8. See 6.
9. See 4.
10. See 4.

Interactions:

1. Concomitant use with acetylsalicylic acid or antithrombotic medicines increases the risks of haemorrhage
2. The medicinal product may enhance action of antithrombotic medicines
3. Concomitant use with acetylisalicylic acid, warfarin or thiazides is not recommended
4. Not indicated
5. See 3.
6. Concomitant use with warfarin is not recommended, in case of simultaneous use with acetylsalicylic acid control of patient state is advised
7. See 1.
8. Possible interactions with anticoagulants, antiplatelet medicines, MAO inhibitors, thiazides, trazodone, fluoxetine, buspirone, herbal drugs containing Hypericum perforatum, melatonin, insulin, drugs metabolised by cytochrome P450 3A4
9. Possible interactions with antithrombotic medicines
10. Not indicated

Contraindications:

1.-8. + 9.-10.: Hypersensitivity to components of the medicinal product

Warnings:

1. Not indicated
2. The treatment should be stopped before planned surgery; patients with coagulation disorders or using antithrombotic medicines should not use this medicinal product without medical supervision; increase in frequency of epileptic seizures cannot be excluded
3. Not indicated

4. Not indicated
5. Not indicated
6. The product is not recommended in case of patients showing predispositions to bleedings
7. See 6.
8. The product may cause prolongation of coagulation time
9. Linked to ethanol content
10. See 12.

Combination products:

Combination products with *Ginkgo biloba* and Allium sativum, Panax ginseng, diverse vitamins, Aesculus hippocastanum, Crataegus monogyna and/or Crataegus laevigata, Viscum album, Arnica Montana and Cynara scolymus exist in Poland.

Portugal: Well-established use

1. *Ginkgo biloba* standardised extract (EGb 761) containing 24% of ginkgo heterosides and 6% of terpenes (ginkgolides, bilobalide)

Since when on the market?	pharmaceutical form	Posology / daily dosage
1989	tablets 40 mg oral solution 40 mg/ml	1 tablet 3 times daily 1 ml 3 times daily

Indications:

Peripheral vascular disturbances – arteriopathy of the legs and its trophic complications; distal microcirculation disturbances (Raynaud). Brain vascular disturbances – memory, affectivity, behaviour, vertigo, headaches, and brain circulatory insufficiency; stroke sequels, migraine. Neurosensory and otovestibular disturbances like hearing loss, tinnitus and vertigo.

There were pharmacovigilance actions taken on the medicinal product containing the herbal substance.

Romania: Well-established use

1. Dry extract standardised to 22-27% ginkgoflavonglycosides and 5-7% terpene lactones (ginkgolides and bilobalide); extraction solvent: acetone/water; DER 35-67:1

Since when are the preparations on the market?	pharmaceutical form	Posology / daily dosage
2001	film-coated tablet, containing 40, 80 or 120 mg standardised extract capsule, containing 40 mg standardised extract oral solution, containing 40 mg/ml standardised extract	oral use; 120-240 mg standardised extract per day; min. 8-12 weeks

Indications:

Symptoms associated with cerebral insufficiency, such as memory lost and depression; pathologic cognitive deficiency in the elderly; peripheral arterial occlusive disease in Stage II (intermittent claudication, Raynaud's syndrome, acrocyanosis); neurosensory disorders of vascular origin (vertigo, tinnitus, acuphenes)

Risks:

Patients with known hypersensitivity to *Ginkgo biloba* preparations or to any of the excipients

The herbal substance is not on the market.

Additional comments:

Ginkgo biloba dry extract comply with Ph. Eur. monograph 1827/2008

Spain: Well-established

1. Tanakene
2. Phar Eur monogr
3. Phar Eur monogr
4. Phar Eur monogr

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 1977	solution (4 g/100 ml)	1-1.5 ml 3 times daily
2. 1996	film-coated tablets 70 mg	1 tablet 2-3 times daily
3. 1994	film-coated tablets 40 mg	1 tablet 3 times daily
4. 2003	film-coated tablets 40 mg	1 tablet 3 times daily

Indications:

For all products: Symptomatic treatment of cerebrovascular and peripheral vascular disorders

Spain: Traditional use

1. Powdered herbal substance
2. Powdered herbal substance
3. Powdered herbal substance

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 1990	capsules 180 mg	2 capsules 3 times daily
2. 1992	tablets 460 mg	1 tablet 3 times daily
3. 1998	capsules 400 mg	1-2 capsules 3 times daily

Indications:

For all products: Vertigo, heavy legs, haemorrhoids

Sweden: Traditional use

1. *Ginkgo biloba*, dried leaf, dry extract (DER 30-40:1) acetone 60-65 %
2. *Ginkgo biloba*, dried leaf, dry extract (DER 35-67:1) acetone 60 %
3. *Ginkgo biloba*, dried leaf, dry extract (DER 35-67:1) acetone 60 %
4. *Ginkgo biloba*, dried leaf, dry extract (DER 35-67:1) acetone 60 %
5. *Ginkgo biloba*, dried leaf, dry extract (DER 35-67:1) acetone 60 %

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 2003, reclassified to THMP 2012	film-coated tablets	1 tablet (100 mg of extract per tablet) 1-2 times daily
2. 1998, reclassified to THMP 2012	capsules, hard	1 capsule (59.4 mg extract per capsule) 2 times daily
3. 1997, reclassified to THMP 2012	film-coated tablets	1-2 tablets (50 mg of extract per capsule) 2 times daily
4. 1997, reclassified to THMP 2012	oral solution	15-22.5 ml (1 ml contains 4.9 mg extract) daily
5. 1997, reclassified to THMP 2012	film-coated tablets	1 tablet (38 mg of extract per tablet) 2-3 times daily

Indications:

For all products: Traditional herbal medicinal product for the treatment of long-standing symptoms in elderly people such as difficulties of memory and concentration, vertigo, tinnitus and fatigue. Prior to use other serious conditions should have been ruled out by a physician.
The indications are based solely on experience and use during a long period of time.

Risks:

Contraindications:

Hypersensitivity to the active substance

Special warnings and precautions for use:

The use in children and adolescents under 18 years of age is not recommended because of concerns requiring medical advice.

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 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 two weeks prior to surgery.

In patients with epilepsy, onset of further seizures – promoted by intake of ginkgo preparations – cannot be excluded. It has been argued that this might be associated with the 4´-O-methylpyridoxine content.

Interactions:

The interaction potential of *Ginkgo biloba* has been investigated in several clinical studies. However, [name of product] may not have been studied specifically and it is possible that [name of product] may have a weaker or more pronounced interaction potential.

Ginkgo biloba containing products have in some studies been observed to give a modest induction of drug metabolising enzymes, such as CYP3A4, CYP2C9 and CYP2C19. It cannot be excluded that other co-regulated enzymes, such as UGTs (catalysing glucuronidation) may be induced as well. As induction gives rise to increased synthesis of enzymes, the net result is mild to moderate decreases in the plasma concentrations of the drugs metabolised by these enzymes. Induction is generally very variable

between individuals. The available study results are somewhat contradictory and it has also been observed that CYP3A4 may be mildly inhibited, resulting in a reduced enzyme activity and increased drug levels. As the observed inducing and inhibitory effects are quite small, this is likely not to be of clinical relevance for most drugs, but it may, however, be relevant for drugs with a narrow therapeutic index and in some patients.

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 *Ginkgo 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 *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.

In theory, it cannot be excluded that the effectiveness of oral contraceptives may be slightly reduced in certain individuals, why it is important to have a good compliance to the contraceptive dosing regimen.

Fertility, pregnancy and lactation:

The use should be avoided during pregnancy and lactation as there is isolated evidence to suggest that preparations containing ginkgo can increase susceptibility to bleeding.

Undesirable effects:

Increased risk of bleeding*, palpitations, arrhythmia, restlessness, insomnia, headache, dizziness, gastrointestinal complaints, exanthema, itching, and urticaria.

The frequencies of the adverse effects are not known.

*After longtime treatment with products containing *Ginkgo biloba* extracts, a few cases of bleeding have been reported (no more details on the extracts given in the reports). However, in clinical studies with standardised extracts, no effect on coagulation has been reported.

If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.

The herbal substance is on the market.

There were pharmacovigilance actions taken on the medicinal product containing the herbal substance.

Additional comments:

The following products have been registered according to a previous national registration scheme (so called registered ‘naturmedel’):

Brandname 80 mg (30:1) 2x2, reg Naturmedel 1986

Brandname 40 mg (EGb 761) 1x2-3, reg Naturmedel 1988

Brandname 250 mg 1x3, reg Naturmedel 1989

Slovenia: Well-established use

1. *Ginkgo biloba* leaf dry extract 35-67:1; quantified to flavonoids and terpene lactones (ginkgolides, bilobalides); extraction solvent: acetone 60 % (m/m)

Since when on the market?	pharmaceutical form	Posology / daily dosage
1998	hard capsule containing 40 or 80 mg extract	oral use; 40 mg capsule 3 times daily; 80 mg capsule 2-3 times daily

Indications:

Treatment of symptoms of mild to moderate cerebral insufficiency and peripheral arterial occlusive disease

Risks:

Adverse effects: gastrointestinal problems, headache and hypersensitive reactions

There were no pharmacovigilance actions taken on the medicinal product containing the herbal substance.

Slovakia: Well-established use

1. *Ginkgo biloba* leaf dry extract; 40 mg standardised to 24% ginkgoflavonglycosides and 6% ginkgolides and bilobalide
2. *Ginkgo biloba* leaf dry extract; 40/80/120 mg (35-67:1); 60% acetone (V/V); standardised to 22-27% ginkgoflavonglycosides, 5-7% terpene lactones – of which 2.8-3.4% are ginkgolides A, B and C and 2.6-3.2% bilobalide; content of ginkgolic acid is less than 5 ppm
3. *Ginkgo biloba* leaf dry extract; 40 mg standardised to 24% ginkgoflavonglycosides and 6% ginkgolides and bilobalide

Since when on the market?	pharmaceutical form	Posology / daily dosage
1. 1996	capsule, hard content is not indicated	40 mg 3 times daily
2. 2008	film-coated tablet content is not indicated	dementia syndromes: 120-240 mg daily peripheral occlusive disorder of arteries, vertigo, etc.: 120-160 mg daily
3. 1992	film-coated tablet, oral solution content is not indicated	40 mg 3 times daily

Indications:

1. Age related disorders of blood circulation in brain (problems with concentration, vertigo and tinnitus). Initial disorders of blood perfusion in legs.
2. Symptomatic treatment of organic brain disorders in dementia syndromes. Vertigo of vascular or involution origin. Adjuvant treatment of tinnitus of vascular or involution origin. Extension of

length, that patient (state II of claudicatio intermittens according to Fontaine) is able to walk over without pain.

3. Dementia syndromes. Claudicatio intermittens, Raynaud syndrome, increased capillary fragility. Sensory disorders based on venous insufficiency – hypacusis, vertigo, tinnitus.

Risks:

1. Gastrointestinal disorders, headache, allergic reactions on skin.
2. Gastrointestinal disorders, headache, allergic reactions on skin. Haemorrhage in combination with NSAID.
3. Gastrointestinal disorders, headache, allergic reactions on skin. Palpitations, hypotension, arrhythmias.

There were no pharmacovigilance actions taken on the medicinal product containing the herbal substance.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	food supplements
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Croatia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	food supplements
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Portugal	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no products

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Available literature on *Ginkgo biloba* at the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) and the incoming, on the "call for scientific data for use in HMPC assessment work on *Ginkgo biloba* L., folium" at October 27, 2011, was used for a literature search. For most current publications a literature search in the DIMDI-database XMEDALL was performed. Articles were filtered by using the following terms: *Ginkgo biloba* included in the title, year of publication between 2004 and 2012, Language in English or German and concerning humans. The search was performed at February 22, 2012. Further relevant literature published until time of public consultation has been taken into account.

Only articles found to be relevant for assessment are included in the list of references.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

According to the information specified above the most frequent authorised herbal preparation on *Ginkgo biloba* leaves with "well-established use" is the refined and quantified dry extract (EGb 761) with a DER of 35-67:1 and acetone 60% as extraction solvent. Most clinical trials were conducted with the special extract of *Ginkgo biloba* leaf (EGb 761); therefore a well-established use could be proved.

Based on the data provided by the National Competent Authorities, other *Ginkgo biloba* leaf products have a "traditional use".

- Powdered herbal substance
- *Ginkgo biloba* leaf tincture (1:5); extraction solvent ethanol 60% (V/V)
- *Ginkgo biloba* leaf dry extract, refined (39.6-49.5:1), containing 22.0-27.0% of flavonoids expressed as flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Ethanol 50% (V/V)

The tincture of *Ginkgo biloba* leaves is less then 30 years on the market and consequently the above mentioned products can not be considered for the monograph because a tradition could not be proved.

For a herbal preparation reported to be marketed in Poland (Ginkgo biloba leaf dry extract, refined (39.6-49.5:1), containing 22.0-27.0% of flavonoids expressed as flavone glycosides, 2.8-3.4% of ginkgolides A, B and C, 2.6-3.2% of bilobalide; extraction solvent: Ethanol 50% (V/V)) the tradition for 30 years was not regarded to be established – initially the extract was not refined, further steps were introduced during 80ies and 90ies in order to achieve quantification and the composition of the relevant preparation changed.

2.2. Information on traditional/current indications and specified substances/preparations

For the traditional powdered herbal substance the wording of the indication was discussed. The agreement is as follows: "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". The use for vertigo and haemorrhoids does not seem to be supported in France anymore, from the preliminary results of an ongoing re-evaluation.

Blaschek *et al.* (2011) describes that *Ginkgo biloba* leaves are used in traditional Chinese medicine (TCM) for the treatment of asthma, hypertension, tinnitus and angina pectoris and in France for chronic venous insufficiency.

The **monograph of the commission E (1994)** approved in Germany the use of undefined *Ginkgo biloba* leaf preparations for disturbed arterial and cerebral blood flow, vertigo, improvement of blood circulation and strengthening of the vessel system, particularly of the veins, as circulation stimulating and exonerative agent and as "psychotropic drug" and "neurotropic drug". The efficacy of the preparations in the mentioned indications has not been proved.

The corresponding monograph on the refined and quantified extract of *Ginkgo biloba* leaves (DER 35-67:1) described the use for the symptomatic treatment of brain-related impairment of mental performance, as part of an overall therapeutic strategy in dementia syndromes with the following main symptoms: memory deficit, disturbance in concentration, depressive mood, dizziness, tinnitus, and headache. The main target group includes patients with dementia syndrome, presenting with primary degenerative dementia, vascular dementia or mixed forms of both. Furthermore, it is used for improving pain-free walking distance in patients with Fontaine Stage II peripheral arterial occlusive disease (intermittent claudication), as part of physiotherapy, including gait training, for vertigo and for tinnitus of vascular and involutive origin.

The **ESCOP monograph (2003)** described the use of *Ginkgo biloba* leaf for the symptomatic treatment of: mild to moderate dementia syndromes including primary degenerative dementia, vascular dementia and mixed forms; cerebral insufficiency; for neurosensory disturbances such as dizziness/vertigo and tinnitus; for enhancement of cognitive performance; and for symptomatic treatment of peripheral arterial occlusive disease (intermittent claudication).

The British Herbal Compendium **(Bradley 2006)** listed the following indications for *Ginkgo biloba* leaf: Symptomatic treatment of mild to moderate dementia including primary degenerative dementia of the Alzheimer type, multi-infarct dementia and mixed forms; treatment of symptoms, attributed to impaired cerebral blood flow and loosely described as cerebral insufficiency, such as difficulties of concentration and memory, confusion, lack of energy and initiative, depressive mood and anxiety; enhancement of cognitive performance in healthy individuals; neurosensory disturbances such as vertigo and certain types of visual dysfunction; conclusions regarding the efficacy of ginkgo in tinnitus are conflicting; a recent meta-analysis of controlled studies revealed no significant benefit; and symptomatic treatment of peripheral arterial occlusive disease (intermittent claudication).

WHO monograph (1999) referred to the Commission E monograph on refined and quantified extract of *Ginkgo biloba* leaves.

DeFeudis (1998) reported that the internal use of *Ginkgo biloba* leaves for medical purposes was first mentioned by Liu Wen-Tai in the "Ben Cao Pin Hue Jing Yaor" (1505 A.D). In modern Chinese pharmacopoeias *Ginkgo biloba* is used for treating dysfunctions of the heart and lungs. The leaves are prescribed for atherosclerosis, angina pectoris, high serum cholesterol levels, dysentery and filariasis as they improve blood circulation, benefit the brain, and are astringent to the lungs.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

See section 1.2.

For the powdered herbal substance the recommended duration of use was discussed and agreed to be for 2 weeks, in line with the duration agreed for Melilotus (and generally accepted for OTC drugs). The duration of use agreed for Vitis (4 weeks) was based on clinical data, available for the preparations concerned.

3. Non-Clinical Data

Many pharmacological studies have demonstrated that *Ginkgo biloba* extracts and its constituents display many properties *in vivo* and *in vitro*. A systematic review of all these studies was not attempted here, rather a selection of studies with emphasis on studies with relevance for the clinical efficacy were reviewed (for a more extensive review, see **Yoshikawa *et al.* (1999)**, **Chan *et al.* (2007)**, **McKenna *et al.* (2001)** and **DeFeudis (1998)**). Further findings from pharmacological and pharmacokinetic studies on humans are available and are discussed in section 4.1.

Yoshikawa (1999) reported the following pharmacological effects of *Ginkgo biloba*:

- An antioxidant action as a free radical scavenger
- Relaxing effect on vascular walls
- An antagonistic action on platelet-activating factor (PAF)
- Improvement of blood flow or microcirculation
- Stimulating effect on neurotransmitters

DeFeudis (1998):

- Actions on the central nervous system
- Effects on behaviour, learning and memory, and recovery from traumatic brain injury
- "Stress-alleviating" action
- Actions on neurosensory systems
- Actions on the cardiovascular system
- Actions on transmembrane ion channels, ionic shifts, and electrical activity of single cells
- Actions on formed elements of the blood
- Actions on other organs, tissues and cells

- Free radical-scavenging, antioxidant, and related mechanisms of action

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The flavones glycosides and the terpene lactones (ginkgolide A, B, C and bilobalide) are considered as the relevant constituents for pharmacological effects in *Ginkgo biloba* leaf preparations. Most pharmacological studies have been performed using a refined and quantified dry extract of *Ginkgo biloba* leaf (EGb 761). Investigations conducted with other *Ginkgo biloba* leaf preparations are stated explicitly.

3.1.1. Primary pharmacodynamic

Antioxidant action

McKenna *et al.* (2001) reviewed an article were cultured rat primary mixed hippocampal cells exposed to reactive oxygen species generated by nitric oxide inducers were completely protected from an accumulation of free radicals and decreased cell survival from co-treatment with either EGb 761 (10-100 µg/ml) or the flavonoids fraction of EGb 761 (25 µg/ml), but not from co-treatment with the terpene lactone constituents.

Improvement of blood flow or microcirculation

Winter (1998) investigated the effects of chronic administration of EGb 761 on brain function in the rat. At approximately 2 months of age, treatment with either EGb 761 (n=10) or vehicle (n=20) was begun and continued five times per week for the life of the subjects who were tested in a radial maze throughout this period. For the first 24 months, EGb 761 rats drank 3 ml solution containing a dose of 50 mg/kg of EGb 761 (HED=8 mg/kg, which corresponds to 480 mg per single dose in a 60 kg human being) in sweetened condensed milk diluted 2:1 in tap water. Control rats drank 3 ml of sweetened condensed milk diluted 2:1 with tap water. Subjects were tested in an eight-arm radial maze for continuous learning and delayed nonmatching to position. Chronic postsession administration of EGb 761 at a dose of 50 mg/kg had no effect on continuous learning but the same dose given presession resulted in fewer sessions to reach criterion performance as well as fewer errors. In addition, chronically EGb 761-treated rats lived significantly longer than vehicle-treated subjects. In a delayed nonmatching to position task using a 30-min delay in 20-month-old rats, EGb 761 administered presession produced a dose-related decrease in total, retroactive, and proactive errors in a delayed nonmatching to position task. At the age of 26 months the group was divided in two with half receiving 200 mg/kg EGb 761 (HED=32 mg/kg, which corresponds to 1920 mg per single dose for a 60 kg human being) presession and the other half vehicle. A statistically significant positive effect of treatment with EGb 761 was observed.

Lin *et al.* (2003) investigated the effect of EGb 761 and a native ginkgo leaf extract (made in China from native ginkgo leaves by the Soxhlet extraction method with 95% of ethanol) on the memory motor functions of rats with chronic cerebral insufficiency (produced by bilateral common carotid artery ligation). The animals were divided into 4 groups. Rats in group 1, 2 and 3 received bilateral common carotid artery ligation. The animals in group 1 were fed with the Chinese ginkgo leaf extract (25 mg/kg, n=6) and the animals in group 2 were fed with EGb 761 (25 mg/kg, n=6). The HED of the administered dose is 4 mg/kg, which complies with 240 mg/kg per single dose for a 60 kg human being. Ginkgo leaf extract, solved in the drinking water, was given orally with syringes once daily after operation. The rats in group 3 did not receive ginkgo leaf extract (n=6). Group 4 was the sham operation group, which received neither bilateral common carotid artery ligation (operation was performed in the same way, except that the common carotid arteries were exposed but not ligated)

nor ginkgo leaf extract (n=4). After the operation memory and motor functions were tested for over 80 days. Spatial memory was tested with an 8-arm radial maze test and motor function was tested using two parameters (locomotor activity and the muscle force of the hind limbs). The results indicate that both *Ginkgo biloba* extracts improved spatial memory from the second week after operation, but only EGb 761 delayed deterioration of motor functions from the fifth week after operation.

Li *et al.* (2003) investigated hippocampal neuron survival/growth and gene expression after prenatal exposure of rats to EGb 761. Pregnant rats received orally administered EGb 761 (100 or 300 mg/kg/day) for 5 days (HED=16 or 48 mg/kg, which correspond to 960 or 2880 mg per single dose in a 60 kg human being). The number of hippocampal neurons of their fetuses increased. Moreover, it was shown that treatment of pregnant rats with EGb 761 (25, 50 or 100 mg/kg/day for 5 days) altered the expression of 187 genes in the hippocampi of male fetuses and 160 genes in those of female fetuses. Using gene-cluster analysis, these genes were grouped into 18 distinct clusters for males and 17 distinct clusters for females. Among these clusters, 35 genes shared a common expression pattern in male and female hippocampal development. Of these genes, changes were confirmed by quantitative real-time polymerase chain reaction (PCR) for genes that are mainly involved in neuronal development, maturation and repair. These molecular and genetic results indicate that EGb 761 increase neuronal survival and alter the expression of specific genes in the developing hippocampus.

In the review by **Chan *et al.* (2007)** it is stated that *Ginkgo biloba* leave extract can protect against the effects of neural damage. It is unclear whether the neuroprotection is from a direct action on the neurons or from an indirect effect from modulation of blood flow and antioxidant action. When *Ginkgo biloba* leave extract was injected (no route of administration or concentration is stated in the review) into rats after global forebrain ischemia, local cerebral blood flow was significantly elevated. Furthermore, *Ginkgo biloba* leaf extract can improve blood flow by increasing red blood cell deformability and decreasing red cell aggregation, and thus, improves red blood cell fluidity and decreases whole blood viscosity (no route of administration or concentration is stated in the review).

Inhibitory action on PAF

Koch (2005) confirmed the results of Akiba *et al.* (1998) principally in a more recent study. The PAF-antagonistic activities of individual ginkgolides and EGb 761 were evaluated in rabbit platelets. PAF-mediated aggregation of human platelets was half-maximally inhibited (IC_{50}) by ginkgolide A, B, C and EGb 761 at concentrations of 13.7, 1.6, 33.2 µM and 23.2 µg/ml, respectively. Of the ginkgolides tested, ginkgolide B exerted by far the most powerful antagonistic effect.

Akiba *et al.* (1998) investigated the effect of *Ginkgo biloba* leaf extract on rabbit platelet aggregation. Purified ginkgolide A, B and C, which are known to be potent platelet-activating factor (PAF) receptor-antagonists, apparently inhibited PAF-induced platelet aggregation, but not oxidant-induced aggregation. An extract of *Ginkgo biloba* leaves (24% flavonol glycosides and 6% terpene lactones (2.4% bilobalide and 2, 0.8, and 1% ginkgolides A, B, and C, respectively)) also inhibited PAF-induced platelet aggregation. The IC_{50} for ginkgolide A, B, C and the extract were determined to be 1.8, 0.5, 32 µM and 31 µg/ml, respectively.

3.1.2. Secondary pharmacodynamic

In the review by **DeFeudis *et al.* (2003)** it was stated that recent studies conducted with various molecular, cellular and whole animal models have revealed that leaf extracts of *Ginkgo biloba* may have anticancer properties that are related to their antioxidant, anti-angiogenic and gene-regulatory actions. The antioxidant and associated anti-lipoperoxidative effects of ginkgo extracts appear to involve both their flavonol glycoside and terpene lactone constituents. The anti-angiogenic activity of

the extract may involve their antioxidant activity and their ability to inhibit both inducible and endothelial forms of nitric oxide synthase. Flavonol glycoside and terpene lactone constituents of ginkgo extracts may act in a complementary manner to inhibit several carcinogenesis-related processes, and therefore the total extracts may be required for producing optimal effects.

3.1.3. Safety pharmacology

In vitro studies

Auguet *et al.* (1982a) EGb 761 (100 µg/ml) that did not provoke contractions of rabbit aorta, potentiated the contractile effect of norepinephrine (EC_{50} from 75 to 36 nM), but had no obvious action on the contractile effects of serotonin and dopamine. These results indicate that low concentrations of EGb 761 might influence catecholaminergic systems by an indirect mechanism.

Auguet *et al.* (1982b) showed that in rabbit isolated aorta EGb 761 induced a concentration-dependent contractile response with an EC_{50} of about 1.0 mg/ml. This action was antagonised by phentolamine. Inhibitors of catecholamine re-uptake, cocaine and desipramine inhibited the contractile effect of EGb 761. Using aortic strips prepared from reserpine-treated (resperine alleviate catecholamine availability) rabbits decreased the response to EGb 761. This indicates that the contractile action of EGb 761 on the rabbit aorta is mediated, at least in part, by release of catecholamines from endogenous tissue stores.

Hellegouarch *et al*. (1985) showed that EGb 761 elicited in a dose-related manner contractions in stripes of rabbit isolated vena cava with an EC_{50} of about 86 µg/ml. Phenoxybenzamine, which is an α-adrenoceptor blocker, blocked the effect of EGb 761 by about 50%.

Peter *et al.* (1966) Spasms of isolated guinea pig ileum were induced by histamine and barium chloride. The spasmolytic effect induced by histamine was abolished with 12 and 40 µg/15ml (=0.8 and 2.7 µg/ml) *Ginkgo biloba* flavonoid preparation to 50 and 100%, respectively. The same effect was observed with 120 µg/15 ml (=8 µg/ml) kaempferol and 200 µg/15 ml (=13 µg/ml) quercetin. Induction of spasms by barium chloride showed the same results, indicating a direct action on the muscle that is supposed to be responsible for vasodilatation.

Vilain *et al.* (1982) studied in more detail the effects of EGb 761 on isolated guinea pig ileum. At a concentration of 50 µg/ml, EGb 761 was either inactive, or produced a slight relaxation. At 100 µg/ml a distinct relaxation was produced, and at 200 µg/ml this relaxation phase was followed by a slight contraction. A biphasic effect, a pronounced relaxation followed by a pronounced contraction, was most evident with 400 µg/ml of EGb 761. With a concentration of 1 mg/ml of EGb 761 the duration of the relaxation phase was decreased while the contraction phase was maintained, and at 3 mg/ml the relaxation phase was practically non-existent while contraction was maintained. Droperidol prolonged the relaxation produced by EGb 761 and cyproheptadine and diphenhydramine usually prolonged the duration of the relaxation and decreased the amplitude of the contraction. Phentolamine, hexamethonium, picrotoxin, methysergide and cimetidine did not affect the response of the ileum to EGb 761.

In vivo studies

Peter *et al.* (1966) examined further the influence of *Ginkgo biloba* flavonoid preparation (diluted in Cremophor EL and intra-arterial injected) on blood pressure in cats, rabbits, rats and guinea pigs.

Cats received consecutively in approx. 15-20 min interval 330 µg/kg, 1 mg/kg, and 3.3 mg/kg flavonoid preparation per 0.5 ml solution/kg with 1 ml/min. There were no changes in blood pressure

or breathing rate. Heart rate was increased by 9% at the high dose. Analogue to these results, no effects on blood pressure, heart and breathing frequency were gained in rabbits.

Oppositional results were observed in rats and guinea pigs. In rats, at the low (330 µg/kg) and high dose (3.3 mg/kg) blood pressure increased by 6 and 28%, respectively for about 13 min with a low rise of heart rate (7%) and a more pronounced rise in breathing rate (13 and 10%, respectively). In guinea pigs, an initial short increase on blood pressure (7%) at the low dose was observed followed by a decrease of 23% for 11 min. Heart rate dropped by 11% and breathing rate increased by 56%. A 10-fold higher dose caused at first increase in blood pressure (48%) for 3 min and a subsequent decrease of 21% for about 13 min. This was accompanied by reduction in heart rate of 16% for 15 min and a rise in breathing rate of 48%. The increase in breathing rate was affected by intravenous injection itself and not by the specific effect of the ginkgo preparation. This was shown in control experiments with the same amount of physiological sodium chloride solution.

Experiments with only Cremophor EL resulted in a rise of blood pressure (between 20 and 50%), heart frequency (8%) and breathing rate (100%).

Brunello *et al.* (1985) Oral treatment of rats with EGb 761 (100 mg/kg/day, p.o., HED for a 60 kg human=968 mg/day) elicited a biphasic effect on the norepinephrine metabolite normetanephrine (NMN) content in the cerebral cortex: An initial decrease was evident after 45 min. followed by a marked increase that was evident after 14 days. Chronic treatment with EGb 761 reduced the density of β-adrenoceptor (no subtype specified) binding to cerebral cortex and β-adrenergic-stimulated adenylate cyclase activity after 2 months. Thus, an increase in norepinephrine levels is inducing β-adrenergic receptor regulation and functional activity.

Kehr *et al.* (2012) The effect of repeated oral administration of EGb 761 and some of its characteristic constituents on extracellular levels of dopamine (DA), noradrenaline (NA), serotonin (5-HT), acetylcholine (ACh) and the metabolites 3,4- dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the medial prefrontal cortex (mPFC) of awake rats was investigated by use of *in vivo* microdialysis technique. Subacute (14 days, once daily), but not acute, oral treatment with EGb 761 (100 and 300 mg/kg) or the flavonoid fraction, which represents about 24% of the whole extract caused a significant and dose-dependent increase in extracellular DA levels in the mPFC. Repeated administration of EGb 761 also caused a modest but significant increase in the NA levels, whereas the concentrations of 5-HT and those of the metabolites DOPAC, HVA and 5-HIAA were not affected. The same treatment regimen was used in a subsequent study with the aim of investigating the effects of two Ginkgo-specific acylated flavonols, 3-O- (2''-O-(6'''-O-(p-hydroxy-trans-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl)quercetin (Q-ag) and 3-O-(2''- O-(6'''-O-(p-hydroxy-trans-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl)kaempferol (K-ag). Both compounds together represent about 4.5% of the whole extract. Repeated oral treatment with Q-ag (10 mg/kg) for 14 days caused a significant increase in extracellular DA levels of 159% and extracellular acetylcholine (ACh) levels of 151% compared to controls. Similarly, administration of K-ag (10 mg/kg) induced a significant rise of DA levels to 142% and ACh levels to 165% of controls, whereas treatment with isorhamnetin, an O-methylated aglycon component of EGb 761 flavonol glycosides had no effect. None of the tested flavonoids had a significant effect on extracellular DOPAC and HVA levels. The effect on neurotransmitter levels seems not to be a general effect of flavonols but rather to be a specific action of acylated flavonol glycosides which are present in EGb 761. The direct involvement of these two flavonol derivatives in the increase of dopaminergic and cholinergic neurotransmission in the prefrontal cortex may be one of the underlying mechanisms behind the reported effects of EGb 761 on the improvement of cognitive function.

3.1.4. Pharmacodynamic interactions

No specific data on pharmacodynamic interactions in animals are reported, as there are various clinical data on this topic.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The whole *Ginkgo biloba* leaf extract represents the active substance. Because the extract consists of a lot of constituents (known only in part), pharmacokinetic studies can only apply to certain constituents. The quantified constituents of the Ginkgo extract are the following: flavonoid glycosides, ginkgolides A, B and C, and bilobalide. The extract contains less than 5 ppm ginkgolic acids.

3.2.1. Absorption

Moreau *et al.* (1986) studied the absorption of radiolabelled ^{14}C EGb 761 in rats. They let Ginkgo plants grow under supply of ^{14}C-acetate. The absorption of the radiolabelled EGb 761 was estimated to be at least 60%. A site of absorption in the upper gastrointestinal tract is suspected since specific radioactivity in blood peaked after 1.5 hours.

3.2.2. Distribution

Moreau *et al.* (1986) further analysed the distribution of radiolabelled EGb 761. The pharmacokinetics of the extract, based on blood specific activity data versus time course, were characteristic of a two-compartment model with an apparent first order phase and a biological half-life of approximately 4.5 hours. During the first 3 hours, radioactivity was preliminary associated with the plasma, but through a gradual uptake after 48 hours. The specific activity in erythrocytes matched that of plasma. Glandular and neuronal tissues and eyes showed a high affinity for the labelled substance.

3.2.3. Metabolism

Chatterjee *et al.* (2005) investigated the effects of EGb 761 on hepatic CYP450 in rats (no subtypes mentioned). Oral administration of EGb 761 (100 mg/kg/day, HED for a 60 kg human=968 mg/day) for 4 days strongly increased liver CYP450 content and altered the ex-vivo biotransformation of androstendione, as well as metabolism of endogenous steroids. However, no effect on the urinary steroid profile was observed in man after intake of 240 mg/day EGb 761 for 28 days. In view of these results, the authors concluded that the effects of EGb 761 on drug metabolism enzymes are specific for rats and may not be extrapolated to man.

Gaudineau *et al.* (2004): The following study was conducted to examine the inhibition of CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4 by EGb 761 and its constituents. As a general observation, EGb 761 inhibited all the P450s studied except CYP2D6 (K_i>900 µg/ml). The activity of CYP2C9 was the most affected by EGb 761 (K_i=14±4 µg/ml). CYP1A2 (106±24 µg/ml), CYP2E1 (127±42 µg/ml), and CYP3A4 (155±43 µg/ml) were also inhibited but to a lesser extent. The terpenoidic fraction inhibited only CYP2C9 (K_i =15±6 µg/ml) whereas the flavonoidic fraction of EGb 761 showed high inhibition of CYP2C9, CYP1A2, CYP2E1, and CYP3A4 (K_i's between 4.9 and 55 µg/ml).

Von Moltke *et al.* (2004): The *in vitro* study was used to determine whether any of 29 constituents of *Ginkgo biloba* can be considered as potentially important inhibitors of any of the five major CYP isoforms in human liver microsomes. Significant inhibitory activity was observed for the flavonol aglycones (kaempferol, quercetin, apigenin, 4´-OH-methyl apigenin, myricetin, tamarixetin), which

yielded IC_{50} values for CYP1A2 or CYP3A of less than 10 µg/ml. Quercetin was also a strong inhibitor of CYP2C9 (IC_{50}=7.8 µg/ml, 25.8 µM), as was myricetin for CYP2D6 (IC_{50}=9.6 µg/ml, 30.2 µM). An inhibitory effect on CYP2C9 and CYP3A was also observed for amentoflavone, sesamin, (Z,Z)-4,4´-(1,4-pentadiene-1,5-diyl)diphenol and 3-nonadec-8-enyl-benzene-1,2-diol. The principal components of *Ginkgo biloba* (terpene lactones and flavonol glycosides) showed no significant inhibition of these human CYPs *in vitro*. It was concluded that a number of flavonol aglycones, as well as the biflavonol amentoflavone, are inhibitors of several human CYP isoforms *in vitro*. Inhibition of CYP2C9 is of potential concern, since this enzyme is responsible for clearance of some drugs (such as S-warfarin) that have narrow therapeutic ranges in clinical practice. The importance of the *in vitro* findings requires evaluation in clinical studies.

3.2.4. Elimination

Moreau *et al.* (1986) examined beside the absorption and distribution also the elimination of radiolabelled EGb 761. Three hours after oral administration of the extract to rats expired ^{14}C-CO_2 represented 16% of the administered dose and 38% after 72 hours. Further 21% were eliminated in the urine and 29% in faeces.

3.2.5. Pharmacokinetic interactions with other medicinal products

Ohnishi *et al.* (2003) examined the effects of a *Ginkgo biloba* leaf extract on the pharmacokinetics of diltiazem, a substrate for CYP3A in rats. *Ginkgo biloba* leaf extract was manufactured in Japan and contained over 24% flavonol glycosides and 6% terpene lactones and less than 1 ppm ginkgolic acids. It contained 1.8% ginkgolide A, 0.85% ginkgolide B, 1.09% ginkgolide C and 2.32% bilobalide. The addition of ginkgo extract to small intestine and liver microsomes inhibited the formation of N-demethyl-diltiazem, a metabolite of diltiazem produced by CYP3A4, in a concentration-dependent manner *in vitro*, with an IC_{50} of about 50 and 182 µg/ml, respectively. A single oral administration of 20 mg/kg (HED=194 mg per single dose) ginkgo extract decreased transiently both, the rate of formation of this metabolite and total amount of CYP in intestinal or hepatic microsomes. Pretreatment with ginkgo extract significantly decreased the terminal elimination rate constant and increased the mean residence time after 3 mg/kg intravenous applied diltiazem. The authors concluded that these results indicated that the concomitant use of *Ginkgo biloba* leaf extract in rats increased the bioavailability of diltiazem by inhibiting both intestinal and hepatic metabolism, at least in part, via a mechanism-based inhibition of CYP3A.

Yoshioka *et al.* (2004a) studied the ability of *Ginkgo biloba* leaf extract to influence the pharmacokinetics of nifedipine, a substrate of CYP3A, in rats. Oral treatment with 20 mg/kg (HED=194 mg per single dose) *Ginkgo biloba* leaf extract with simultaneous intravenous administration of 2.5 mg/kg nifedipine did not affect pharmacokinetic parameters. However, maximum plasma nifedipine concentration, the area under the concentration-time curve and absolute bioavailability after oral administration of 5 mg/kg nifedipine were significantly reduced by simultaneous oral treatment with *Ginkgo biloba* leaf extract. The conclusion of the authors is that these results suggest that the concomitant oral use of *Ginkgo biloba* leaf extract appeared to reduce the first-pass metabolism of orally administered nifedipine by inhibiting CYP3A in rats.

Hellum *et al.* (2008) investigated *Ginkgo biloba* (solubilised in ethanol) for its *in vitro* inhibitory potential of CYP3A4 mediated metabolism and P-glycoptrotein (P-gp) efflux transport activity. C-DNA baculovirus expressed CYP3A4 and Caco-2 cells were used. Ketoconazole and verapamil were applied as positive control inhibitors, respectively. A validated HPLC methodology was used to quantify the formation of 6-OH-testosterone and scintillation counting was used to quantify the transport of ^{3}H-digoxin (digoxin is a recommended and established substrate for P-gp transport experiments in Caco-2

cells). *Ginkgo biloba* inhibited CYP3A4 activity (IC_{50} value of 668±66 µg/ml) and P-gp activity (IC_{50} value of 23.6 µg/ml). The low IC_{50} value for *Ginkgo biloba* may indicate an inhibition of P-gp in the small intestine *in vivo*.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

In crude Ginkgo extracts a group of alkylphenols (e.g. ginkgolic acids, ginkgol, bilobol) has been described to exhibit potential contact allergenic and toxic properties. A maximum concentration of 5 ppm has to be maintained to comply with the Ph. Eur. and to ensure safety of use for *Ginkgo biloba* leaf extracts.

3.3.1. Single dose toxicity

Ginkgo biloba extract

DeFeudis (1998) reports of acute toxicity data. Therefore, the LD_{50} values in mice are 7.73, 1.1 and 1.9 g/kg by oral, i.v. and i.p. administration of EGb 761, respectively. LD_{50} values for rats are comparable with 1.1 and 2.1 g/kg by i.v. and i.p. EGb 761 administration. Acute toxicity of orally administered EGb 761 in the rat was not determinable because the extract showed until a dose of 10 g/kg no lethal effects. Higher doses could not be administered.

Isolated compounds

Leistner and Drewke (2010) reviewed recent experiences with *Ginkgo biloba* and its derived products with a view to ginkgotoxin. Known from reported cases of intoxication, at sublethal doses, symptoms of poisoning are eleptiformic seizures, unconsciousness, and paralysis of the legs. A dosage of 11 mg/kg of the isolated ginkgotoxin triggered seizures in guinea pigs. Administration of 30 to 50 mg/kg ip was followed by atrioventricular block or ventricular fibrillation and death of the animals. An LD_{50} of ca. 30 mg/kg ip was determined for a rabbit. A higher dose of 400 to 600 mg/kg ip was needed to elicit convulsions in rats. Ginkgotoxin is a constituent of *Ginkgo biloba* seeds and leaves. Accordingly, extracts derived from dried *Ginkgo biloba* leaves contain ginkgotoxin. A HPLC analysis revealed that different allopathic medications offered by various companies contain between 11.4 and 58.62 µg of ginkgotoxin in a recommended maximum daily dose (120-240 mg). The presence of ginkgotoxin in *Ginkgo biloba* products raises the question if this could cause any undesirable health effects such as seizures. Assuming in a worst case scenario that all ginkgotoxin (58.6 µg) taken up by one daily dose ends up in the blood serum, a concentration of ginkgotoxin in human plasma of 53 to 80 nM calculated for 6 or 4 L of blood, respectively, would result. This is on the same order of magnitude as vitamin B_6 levels in blood plasma, which are reported to be 114 nM. At present it cannot be ruled out that *Ginkgo biloba* medicinal products may lower the threshold for seizures in epileptic patients.

Liu and Zeng (2009) investigated the cytotoxicity of ginkgolic acid (15:1, prepared in own laboratory and determined by the LC-MS method, purity >99%) using *in vitro* bioassay systems. First, cytochrome P450 enzymes involved in ginkgolic acid metabolism were investigated in rat liver microsomes. Then, two *in vitro* cell-based assay systems, primary rat hepatocytes and human hepatoma cells HepG2, were used to study and the measurement of MTT reduction was used to assess cell viability. Results indicated that the cytotoxicity of ginkgolic acid in primary rat hepatocytes was lower than in HepG2 cells. Ginkgolic acid was demonstrated less cytotoxicity in four-day-cultured primary rat hepatocytes than in 20-hour cultured ones. Co-incubation with selective CYP inhibitors, α-naphthoflavone and ketoconazole, could decrease the cytotoxicity of ginkgolic acid in primary rat hepatocytes. Consequentially, pretreament with selective CYP inducers, β-naphthoflavone and

rifampin, could increase the cytotoxicity of ginkgolic acid in HepG2 cells. These results suggest that HepG2 cells were more sensitive to the cytotoxicity of ginkgolic acid than primary rat hepatocytes, and CYP1A and CYP3A could metabolise ginkgolic acid to more toxic compounds.

3.3.2. Repeated dose toxicity

Ginkgo biloba extract

Salvador (1995) reported of no chronic toxicity. There was no evidence of organ damage or impairment of hepatic and renal functions when EGb 761 was administered orally to rats and mice over a period of 27 weeks in doses ranging from 100 to 1,600 mg/kg.

DeFeudis (1998) stated that chronic toxicity studies in the rat (27 weeks) and dog (26 weeks), conducted with EGb 761 doses of 20 and 100 mg/kg/day initially and then gradually increased to 300, then 400 and 500 mg/kg/day in rats and to 300, then 400 mg/kg/day in dogs, showed no evidence of organ damage and no impairment of hepatic or renal function.

Isolated compounds

Hecker *et al.* (2002): The cytotoxic potential of ginkgolic acids was assessed in this *in vitro* study. Test subjects were the human keratinocyte cell line HaCaT and the rhesus monkey kidney tubular epithelial cell line LLC-MK_2. The influence of a defined mixture of ginkgolic acids on cell growth, viability, integrity and morphology was investigated in more detail. EGb 761, which contains less than 5 ppm ginkgolic acids, was used as reference substance. The results confirm, that ginkgolic acids, which are basically removed during production of the standardised extract EGb 761, carry a considerable cytotoxic potential. As shown by the neutral red uptake assay, ginkgolic acids strongly reduce the number of viable cells, whereas EGb 761 displayed a much lower activity in this test system. The IC_{50} values in HaCaT and LLC-MK_2 cells after incubation with EGb 761 were 889 mg/l and 1481 mg/l, respectively. For the test mixture the IC_{50} concentrations in HaCaT and LLC-MK_2 cells were 22 mg/l and 4.6 mg/l, respectively. A concentration dependent release of LDH was observed when cells were incubated in the presence of ginkgolic acids (1-100 mg/l). In contrast, even at a concentration of 1800 mg/l EGb 761 did not cause release of LDH above controls. Since ginkgolic acids interacted with the assay for acid phosphatise (ACP), no index of lysosomal damage could be established by this method. Incubation of HaCaT cells with ginkgolic acids for 18 h increased the proportion of apoptotic cells from about 6% (control) to nearly 80% at concentrations of ≥30 mg/l. Electron microscopic analysis of HaCaT cells revealed a drug induced formation of myelinosomes possibly due to the inhibition of lysosomal enzymes, while morphological evaluation of LLC-MK2 cells indicated that the cytotoxic activity of ginkgolic acids in these cells is primarily mediated by transformation of mitochondria, which is probably induced by uncoupling of oxidative phosphorylation.

3.3.3. Genotoxicity

A *Ginkgo biloba* leaf extract was tested positive for gene mutations in bacteria and equivocal and negative for chromosome mutations in two separate in vivo tests in peripheral erythrocytes and bone marrow cells in mouse. (NTP Technical report 578, 2013)

3.3.4. Carcinogenicity

Major findings from NTP report:

NTP Technical report 578 (2013) has tested a *Gingko biloba* leaf extract for carcinogenesis in two year studies in rats and mice.

Summarising the major findings of the NTP Technical report, rodents dosed with *Ginkgo biloba* extract showed increased rates of a variety of lesions in the liver, thyroid gland, and nose. These lesions included hypertrophy in the liver and thyroid gland in rats and mice, liver hyperplasia in male and female rats, hyperplasia and atrophy of the epithelium in the nose of male and female rats.

Increased incidences of cancers of the thyroid gland were seen in female rats and liver cancers in male and female mice.

Mononuclear cell leukemia was observed in male rats at 300 and 1000 mg/kg. The increased incidence of mononuclear cell leukemia in rats is probably a background finding, as this strain of rats has a highly variable background rate for this tumor.

View of the HMPC based on a detailed assessment of the NTP technical report with respect to the development of a monograph:

No carcinogenicity was observed in the nose, but benign respiratory epithelium tumours (adenoma) were observed in 2 female rats at the intermediate dose level (300 mg/kg). The occurrence of adenoma did not show a dose response and occurred in one sex only. However, there were dose-dependent morphological changes in the nose. It should be noted that these lesions may have been secondary effects from oesophageal reflux due to gavage application and/or a secondary effect to repeated irritant and inflammatory stimulation. To be able to draw a definitive conclusion of the nose findings additional information from the pathology report would be needed. Induction of CYP 450 enzymes in the nose may also have contributed to these lesions. The mechanism of the non-neoplastic lesions in the nose in rodents has not been fully established, and therefore the risk to humans cannot be finally assessed. However, the proposed explanations are plausible and there was no increase of neoplastic changes. Thus, these findings are considered of limited relevance for human safety.

Carcinogenic effects associated with *Ginkgo biloba* extract administration are mostly characteristic of lesions related to hepatic enzyme induction. Carcinogenic activity of *Ginkgo biloba* extract in liver was more pronounced in mice than rats. The relation of thyroid lesions to increased metabolic activity in liver is well known in rodents, and rats are especially sensitive to that mechanism which is in correlation to study results where hepatic effects were more severe in mice that in rats, but thyroid effects were more pronounced in rats (Hernandez *et al*. 2009, Li *et al*. 2009, Silva Lima & van der Laan 2000).

In principle the lesion in thyroid and liver are considered due to promotion by thyroid and liver enzyme induction and not due a genotoxic mode action.

Effects seen in nose olfactory and respiratory epithelium in rat and mouse might be considered related to secondary effects from oesophageal reflux due to gavage application or to induction of metabolising enzymes and be a secondary effect to repeated irritant and inflammatory stimulation or enzyme induction via systemic exposure. Furthermore only adenomas occurred and only in the 300 mg/kg dose female group. However as exposure data of the nasal epithelium are missing there are not enough data for a final conclusion.

Mononuclear cell leukemia observed in the 2-year carcinogenicity study in rats given *Ginkgo biloba* might be considered a background finding and is considered of limited relevance to humans.

The NTP studies do not provide evidence for an increased cancer risk following the use of *Ginkgo biloba* extracts at the approved posology. There is plausible evidence for the main effects in liver and thyroid gland to be caused by rodent specific mechanisms not relevant for humans. For the morphological changes in the olfactory epithelium in female rats, amechanistic explanation has not been demonstrated, although there are plausible explanations proposed. The MCLs in male rats are considered of limited relevance to humans. These effects however were not seen in the low dose

groups providing margins of exposure of at least 5 to 6 compared to the NOEL for these effects based on a mg/m^2 calculation of the human equivalent dose.

Conclusion:

At present there is no proof for an increased cancer risk identified for patients taking Ginkgo medicinal products at their approved posology.

3.3.5. Reproductive and developmental toxicity

Monograph relevant extract

Eimazoudy and Attia (2012) evaluated potential anti-implantation and abortifacient effect of EGb 761 in albino female mice. EGb 761 was orally administered in 0 (control), 3.7, 7.4 and 14.8 mg/kg bw/day (HED=19.8, 39.6, 79.3 mg per daily dose) for 28 days (thereafter mated with normal fertile male), from day 1 to day 7 of pregnancy or from the 10^{th} to 18^{th} day of pregnancy, respectively. Vaginal smears were performed daily. On the 20^{th} day of pregnancy, the females were killed by cervical dislocation and their kidneys, liver, brain, placenta, spleen and ovaries were removed and weighed. The ovaries were prepared for histological examinations, and then ovarian follicles were counted. Maternal toxicity, estrous cycle, reproduction hormones, ovarian follicle counts, resorption index, implantation index, fetal viability and foetuses, and placenta mean weights were evaluated. There was a dose-dependent ovarian toxic effect of EGb 761. Ovarian follicle counts, resorption index, implantation index, fetal viability were significantly reduced in 14.8 mg/kg bw/day dose. Treatment with this dose induced disruption of estrous cycle and caused maternal toxicity, in addition to fetal toxicity.

DeFeudis (1998) reported of studies were oral administration of 100, 400 or 1600 mg/kg/day of EGb 761 to rats and 100, 300 or 900 mg/kg/day to rabbits did not elicit teratogenic effects or affect reproduction.

Rudge *et al.* (2007) evaluated the effect of EGb 761 treatment given orally once a day in a dose of 200 mg/kg (HED=32 mg/kg which corresponds to 1935 mg per daily dose for a 60 kg human being) from day 0 to 20 of pregnancy of streptozotocin-induced diabetic rats. The maternal reproductive performance (not histopathological determined) and the maternal and fetal liver antioxidant systems were examined. Four experimental groups were studied: G1 = non-diabetic untreated rats (control), G2=non-diabetic rats treated with EGb 761, G3=diabetic untreated rats and G4=diabetic rats treated with EGb 761. Maternal and fetal liver samples were obtained for superoxide dismutase (SOD), catalase (CAT), glutathione peroxidise (GSH-Px), and total glutathione (GSH-t) determinations. The diabetic (G3) and treated diabetic (G4) groups of rats presented significant maternal hyperglycemia, reduced term pregnancy rate, impaired maternal reproductive outcome and fetal-placental development, decreased GSH-Px (G3 and G4=0.6±0.2) and SOD (G3=223.0±84.7; G4=146.1±40.8), and decreased fetal CAT activity (G3=22.4±10.6; G4=34.4±14.1) and GSH-t (G3 and G4=0.3±0.2), compared to the non-diabetic groups (G1 and G2). For G1, maternal GSH-Px=0.9±0.2 and SOD=274.1±80.3; fetal CAT=92.6±82.7 and GSH-t=0.6±0.5. For G2, EGb 761 treatment caused no toxicity and did not modify maternal or fetal-placental data. EGb 761 at the nontoxic dose used, failed to modify the diabetes-associated increase in maternal glycemia, decrease in pregnancy rate, decrease in antioxidant enzymes, and impaired fetal development when the rats were treated throughout pregnancy.

Components and other extracts

Shiao and Chan (2009) investigated the effects of ginkgolide B on mouse oocytes maturation, fertilisation, and sequential embryonic development *in vitro* and *in vivo*. Ginkgolide B induced a

significant reduction in the rate of oocyte maturation, fertilisation, and *in vitro* embryonic development. Treatment of oocytes with 1-6 µM ginkgolide B during *in vitro* maturation led to increased resorption of postimplantation embryos and decreased placental and fetal weights. Data obtained using an *in vivo* mouse model further disclosed that consumption of drinking water containing 3-6 µM (estimated daily intake is 325-625 µg/kg with a HED of 29-55 µg/kg, versus human daily intake of 130 µg/kg) ginkgolide B led to decreased oocyte maturation and *in vitro* fertilisation, as well as early embryo development injury, specifically, inhibition of development to the blastocyst stage *in vivo*.

Chan (2005) showed that ginkgolide A and ginkgolide B treatment (both 5 and 10 µM) of mouse blastocysts induces apoptosis, decreases cell numbers, retards early postimplantation blastocyst development, and increases early-stage blastocyst death *in vitro*.

Baron-Ruppert and Luepke (2001) assessed the adverse properties of alkylphenols in different fractions, gained as water insoluble compounds (decanter sludge) during production of EGb 761, for their embryotoxic effects in the hen's egg test (HET). A fraction enriched for ginkgolic acids (16%) and biflavones (6.7%) was found to induce death of 50% of the chick embryos (LD_{50}) at a dose of 1.8 mg/egg (approx. 33 ppm). A similar strong lethal effect was observed for a fraction which contained 58% ginkgolic acids but less than 0.02% biflavones with LD_{50} at a dose of 3.5 mg/egg (64 ppm). In contrast, an extreme low toxic potential was shown in a fraction containing 1% ginkgolic acids and 16% biflavones with LD_{50} at 250 mg/egg or 4540 ppm. Thus, the present investigation confirms the high toxic potential of ginkgolic acids, although it cannot be excluded that biflavones or some other constituents in the different fractions may amplify the adverse effect of these substances. Since no contribution of alkylphenols to the therapeutic efficacy of *Ginkgo biloba* extracts has been confirmed and their elimination during the manufacturing process does not cause technical problems, the authors concluded that these results further support the requirement for the completest possible removal of these compounds under toxicological considerations.

Floissac and Chopin (1999): The effect of *Ginkgo biloba* on embryological development in chick embryos was the subject of this article. Fertile chick eggs (n=387) were injected with one of five dosages of *Ginkgo biloba* (not further specified) diluted in physiological saline. The *Ginkgo biloba* doses were equivalent to single human doses of 20, 40, 80, 120, and 240 mg. Control eggs (n=74) received physiological saline only. On developmental day 7, the embryos were examined for viability and malformations. A trend to decreasing viability with increasing *Ginkgo biloba* dosage was observed, but the trend was not statistically significant. Increasing dosages of *Ginkgo biloba* were accompanied by increasing frequencies of malformations particularly subcutaneous bleeding. Embryos exposed to the three highest dosages of *Ginkgo biloba* had statistically significant increases in total malformations ($p<0.05$) and subcutaneous bleeding ($p<0.05$). These dosages represented the suggested daily dose range for adults. In conclusion it was stated, that *Ginkgo biloba* should be used with caution during pregnancy.

Fernandes *et al.* (2010) verified whether an aqueous *Ginkgo biloba* extract (manufactured in Brazil with the following composition: 28.2% flavonoid glycosides; 8.3% terpene lactones; 15% quercetin; 10.9% kaempferol; 2.3% isorhamnetin; 1.4% ginkgolide A; 1.1% ginkgolide B; 3.0% ginkgolide C; 0.9% ginkgolide J; 0.7% bilobalide and less than 5 ppm (0.81%) of ginkgolic acids) affects embryonic development when administered to pregnant rats during the one-cell-to-blastocyst period, which includes the phase of tubal transit and implantation. Pregnant rats received 0, 3.5, 7.0 and 14.0 mg/kg/day of aqueous *Ginkgo biloba* extract by gavage, from the 1st to the 8th day of pregnancy. No significant toxic effect was found on the maternal organism and for embryonic parameters.

Zehra *et al.* (2010) determined gross structural malformations to the mice fetuses of the mothers given a standardised *Ginkgo biloba* extract (not further specified) during pregnancy. Pregnant females were divided into three groups (A, B and C), of 6 mice each. The two experimental groups A and B

received 78 and 100 mg/kg/day, respectively, whereas group C served as control. Both experimental groups were given the drug orally throughout the gestational period. The animals were sacrified on the 18th day of gestation. Forty-nine fetuses from groups B and C and 50 fetuses from group A were recovered. There was a significant ($p<0.05$) decrease in weight and crown-rump length of fetuses in group B as compared to those from group A and C. Further, fetuses from groups A and C did not show any gross abnormalities, whereas those from group B exhibited a high frequency of malformations including round shaped eye and orbits (48%), syndactyly (40.8%), malformed pinnae (44.1%), nostrils, lips and jaws (all three together 42.8%). These results indicate that *Ginkgo biloba* extract is harmful to the developing fetuses *in vivo*.

Pinto *et al.* (2007) evaluated the effects of a *Ginkgo biloba* extract (composed of 28.2% of ginkgoflavonglycosides; 8.3% of terpene lactones; 15% of quercetin glycosides; 10.9% of kaempferol glycosides; 2.3% of isorhamnetin glycosides and less than 5 ppm of ginkgolic acids) during the periods of organogenesis and fetogenesis. 0, 3.5, 7 and 14 mg/kg body weight/day *Ginkgo biloba* extract was administered orally in 1 ml of aqueous solution to pregnant rats from the 8th to 20th day of pregnancy. After killing the rats on the 21st day the following parameters were evaluated: maternal body weight; food and water intake; maternal's liver, kidney and ovary weights; resorption index; post-implantation loss; mean of live fetuses; fetuses and placenta mean weight; fetuses´liver, kidney, lung and brain weights; fetuses´external malformations. The maternal parameters of toxicity did not changed significantly, whereas the treatment *Ginkgo biloba* extract resulted in a significant decrease in the fetuses mean weights. The results suggest that Gingko biloba extract administration with 7 and 14 mg/kg/day to rats in the organogenic and fetogenic periods can lead to fetal intra-uterine growth retardation, although it did not cause maternal toxicity.

Amin *et al.* (2012) assessed the protective effects of *Ginkgo biloba* extract (GBE, purchased from General Nutrition Corporation, Pittsburgh, USA) against chemotherapeutic-induced reproductive toxicity using a data mining tool, namely Neural Network Clustering (NNC) on two types of data: biochemical & fertility indicators and Texture Analysis (TA) parameters. GBE (1 g/kg/day, HED=9677 mg per daily dose) was given orally to male albino rats for 26 days. This period began 21 days before a single cisplatin (CIS) intraperitoneal injection (10 mg/kg body weight). GBE given orally significantly restored reproductive function. Tested extract also notably reduced the CIS-induced reproductive toxicity, as evidenced by restoring normal morphology of testes. In GBE treated mice the attenuation of CIS-induced damage was associated with less apoptotic cell death both in the testicular tissue and in the sperms. CIS-induced alterations of testicular lipid peroxidation were markedly improved by the examined plant extract. NNC has been used for classifying animal groups based on the quantified biochemical & fertility indicators and microscopic image texture parameters extracted by TA. NNC showed the separation of two clusters and the distribution of groups among them in a way that signifies the dose-dependent protective effect of GBE.

Al-Yahya *et al.* (2006): The effects of *Ginkgo biloba* (50 mg tablet contains 50 mg of *Ginkgo biloba* extract and 12 mg of ginkgo flavone glycosides, which correlates to 24%) on reproductive, cytological and biochemical toxicity was evaluated in Swiss albino mice. The mice received 25, 50 or 100 mg/kg/day oral doses of an aqueous suspension of *Ginkgo biloba* for 90 days. The following parameters were evaluated: reproductive organ weight; motility and content of sperms; spermatozoa morphology; cytology of the testes chromosomes; study on reproduction; biochemical study on proteins, nucleic acids, malondialdehyde (MDA) and nonprotein sulfhydryl (NP-SH). Significant changes were observed in the weight of caudae epididymis, prostate, chromosomal aberrations, rate of pregnancy and pre-implantation loss. The evaluation of biochemical parameters showed depletion of nucleic acids, NP-SH and increase of MDA, which elucidated the role of free radical species in the induced changes in testis chromosomes and the reproductive function.

Ondrizek *et al.* (1999a) analysed the effect of *Ginkgo biloba* (not further specified) at 0.1 and 1 mg/ml on sperm DNA and on the fertilisation process. Zona-free hamster oocytes were incubated for 1 hour in *Ginkgo biloba* or control medium before sperm-oocyte interaction. The DNA of *Ginkgo biloba*-treated sperm was analysed with denaturing gradient gel electrophoresis. Oocyte penetration and integrity of the sperm BRCA1 exon 11 gene were measured as main outcomes. The results show that high concentrations of *Ginkgo biloba* could inhibit the penetration of oocytes by sperm. The oocytes treated with *Ginkgo biloba* were visibly degenerated. There was abnormally high sperm binding on the oocyte surface. The lower concentration of *Ginkgo biloba* produced a numerically lower percentage of penetration, although this was not significant. Antioxidants have been used to prevent oxidative damage to cellular membranes. In this case, however, the antioxidant property of this herb did not help improve sperm penetration. Exposure of sperm to *Ginkgo biloba* had no effect on DNA denaturation.

Ondrizek *et al*. (1999b) analysed sperm motility parameters in the presence of *Ginkgo biloba* (not further specified) at 0.12 and 1.2 mg/ml. Sperm were incubated in *Ginkgo biloba* or control medium and parameters were measured on a Hamilton-Thorn analyser after 1, 4, 24 and 48 hour at 37°C. There were no significant differences in the motility and the kinematic parameters on *Ginkgo biloba* versus the control at the low concentration tested. However, when the concentration of *Ginkgo biloba* was increased sperm motility was inhibited at 24 and 48 hours. Sperm curvilinear velocities were lower after 24 and 48 hours in the high concentration of *Ginkgo biloba* compared with the control. There were no differences in the other remaining kinematic parameters (Hyperactivation and beat cross frequency) for the high concentrations of *Ginkgo biloba*.

3.3.6. Local tolerance

Peter *et al.* (1966) administered rabbits and guinea pigs by intramuscular injections 50 and 200 µg/kg in 0.5 ml solution concentrated *Ginkgo biloba* extract. Injections were well tolerated. Histologically, a moderate to strong oedematous loosening of intact muscle fibres without necroses was noted. At the injection site inflammatory reactions as signs of resorption as well as mild interstitial mesenchymal activation were noted after administration of both *Ginkgo biloba* extract and placebo. No necroses were observed.

After intraarterial administration of 15 mg/kg in 3.0 ml solution concentrated *Ginkgo biloba* extract to rabbits the intima and the media of the arteries were undamaged and unsuspicious. The same results were observed in guinea pigs and cats.

3.3.7. Other special studies

Ahlemeyer *et al.* (2001) questioned whether ginkgolic acids also have, besides allergenic and genotoxic effects, neurotoxic effects. In the presence and in the absence of serum ginkgolic acids caused death of cultured chick embryonic neurons in a concentration-dependent manner. Ginkgolic acids-induced death showed features of apoptosis as chromatin condensation, shrinkage of the nucleus and reduction of the damage by the protein synthesis inhibitor cycloheximide was observed, demonstrating an active type of cell death. However, further indicators of apoptosis (DNA fragmentation detected by the terminal-transferase-mediated ddUTP-digoxigenin nick-end labelling (TUNEL) assay and caspase-3 activation) were not seen after treatment with 150 µM ginkgolic acids in serum-free medium, a dose which increased the percentage of neurons with chromatin condensation and shrunken nuclei to 88% compared with 25% in serum-deprived, vehicle-treated controls. These findings suggest that ginkgolic acid-induced death showed signs of apoptosis as well as of necrosis. Ginkgolic acids specifically increased the activity of protein phosphatase type-2C, suggesting it to play a role in the neurotoxic effect mediated by ginkgolic acids.

3.4. Overall conclusions on non-clinical data

Pharmacodynamic

The pathomechanism of AD and other forms of dementia is still under discussion. According to this, diverse models exist about the development of the most common forms of dementia (degenerative dementia (AD) and vascular dementia). So it is difficult to estimate which model represents the pathomachanism of the disease. But a final conclusion is not possible.

In animal experiments, Ginkgo biloba extract was shown to improve spatial memory deficits in a transgenic mouse model of AD, as well as to improve acquisition of working memory in young and aged rats. However, the precise neurochemical correlates of these behavioral effects of Ginkgo biloba extract are not completely understood.

The pharmacological effect on blood flow or microcirculation, the inhibitory action on PAF as well as an antioxidant action as a free radical scavenger could be supportive of a possible neuroprotective effect.

The pharmacological actions could already be observed at doses which are of clinical relevance as well at doses which were 2-8 folds higher as the human equivalent dose.

The Ginkgo biloba extract EGb 761 contains standardised amounts of flavonoids and ginkgolides. In animal models of Alzheimer's disease (AD), these antioxidants and neuroprotectants inhibit amyloid β42-induced hippocampal neuron dysfunction and death, amyloid β-induced pathological behaviours and amyloid β aggregation, and enhance neurogenesis.

Moreover, EGb 761 and Ginkgo biloba extracts may modulate catecholamine (DA) release in the prefrontal cortex.

These characteristics might generally support a clinical relevance of the above mentioned supposed mechanisms in the pathophysiological process underlying common forms of dementia including AD and VaD.

The results of the safety pharmacology studies indicate that *Ginkgo biloba* extracts are active on venous and arterial preparations *in vitro* (at least in part via release of catecholamines). The effect on isolated guinea pig ileum indicates a direct action on the muscle. Effects on blood pressure, heart rate and breathing rataes are difficult to interpret because of the deviant route of administration and because of the interference with the diluent.

Pharmacokinetic

A set of pharmacokinetic studies are presented mostly for the extract EGb 761. The rate of absorption after oral administration of radiolabelled EGb 761 to rats was estimated to be 60%. The maximum concentration was reached after 1.5 hours.

Especially studies concerning pharmacokinetic drug interactions are mentioned, which were performed using different *Ginkgo biloba* extracts, so the content percentages of active principles are different and in consequence the potential interaction effects described not necessary should be reproducible for the monograph relevant *Ginkgo biloba* preparation.

Oral administration of EGb 761 strongly increased liver CYP P450 content. With regard to the unchanged steroid profile in man, it is assumed that the effects of EGb 761 on drug metabolising enzymes are specific for rats and may not be extrapolated to man. But on the other hand experiments with human liver microsomes have shown that *Ginkgo biloba* leaf dry extract can affect CYP enzymes *in vitro*.

An *in vitro* study indicates that EGb 761 inhibits activity of CYP1A2, CYP2C9, CYP2E1 and CYP 3A4, in which the activity of CYP2C9 was the most affected. Another *in vitro* study with an ethanolic *Ginkgo biloba* extract supports the inhibitory effect on CYP3A4 activity and proposes also an inhibitory effect on P-gp activity. *In vivo* studies in animals confirmed inhibition activity of *Ginkgo biloba* leaf extract on CYP3A4. Nervertheless, some interaction that occurred in the animal assays could not be extrapolated to humans.

Toxicology

A study report on a carcinogenesis study with a Ginkgo biloba extract (different from the Pharm. Eur. Specification but nevertheless similar) in rats and mice for two years raised questions about possible carcinogenic effects.

The NTP studies do not provide conclusive evidence for an increased cancer risk for the use of Ginkgo biloba extracts at the recommended doses. There is plausible evidence for the main effects in liver and thyroid gland to be caused by rodent specific mechanisms not relevant for humans. For adenomas in olfactory epithelium in rats and MCLs in male rats a conclusive mechanistic explanation is currently not provided. These effects however were not seen in the low dose groups providing margins of exposure of at least 5 to 6 compared to the NOEL for these effects based on a mg/m^2 calculation of the human equivalent dose.

It can be concluded that at present there is no proof for an increased cancer risk identified for patients taking Ginkgo medicinal products at their approved posology.

However as any potential of Ginkgo biloba extracts for inducing gene mutations in vivo cannot be excluded due to missing of such data and as there are significant differences in the extract tested in the NTP study and the extract EGb 761, mostly marketed in pharmaceuticals in Europe, with respect to exposure to ginkgolides (LPT Report No. 29879, 2013) in mice, data of in vivo gene mutation assays in target organs of carcinogenesis in mice for Ginkgo biloba extracts are considered necessary to fully exclude any in vivo mutagenic potential of Ginkgo biloba extracts to be involved in the induction of tumors in rodents and further exclude any relevance for human use.

Limited studies concerning single dose and repeated dose toxicity, as well as local tolerance are mentioned above as there is sufficient and well-documented experience available in humans (see section “clinical data”).

The results show LD_{50} values for mice and rats for single dose toxicity. With 7.73, 1.1 and 1.9 g/kg for mice and >10, 1.1 and 2.1 g/kg for rats by oral, i.v. and i.p. EGb 761 administration, respectively. Furthermore, no evidence of organ damage or impairment of hepatic and renal functions by chronic EGb 761 administration in rats, mice and dogs was observed. The data of single dose and repeated dose toxicity of isolated compounds are administered in much higher doses than clinically relevant.

Most of the available reproductive and developmental toxicity studies are conducted with *Ginkgo biloba* extracts different from the monograph relevant extract or with single components present in *Ginkgo biloba* extracts. The studies are conducted *in vitro* as well as *in vivo* in mice, rats, rabbits and chicken. The results of a current investigation showed a dose-dependent ovarian toxic effect of EGb 761 in rats at HED: 20-80 mg per daily dose. The effect on fertility was represented by significantly reduced ovarian follicle counts, resorption index, implantation index and fetal viability. In contrast to these results, older studies indicate no teratogenic effects or reproductive toxicity of EGb 761 orally administered to rats (100, 400 or 1600 mg/kg/day) and to rabbits (100, 300 or 900 mg/kg/day).

In vitro and *in vivo* studies conducted with single components of Ginkgo biloba (ginkgolide A and B with a HED of 29-55 µg/kg versus a human daily intake of 130 µg/kg) indicated significant reduction on oocyte maturation, fertilisation and embryonic blastocysts development. The high toxic potential of

ginkgolic acids and the following completest possible elimination during manufacturing ginkgo extracts was confirmed in an *in vivo* study.

There is evidence that ginkgo containing preparations can increase the disposition for bleeding. Therefore, *Ginkgo biloba* leaf dry extract must not be used during pregnancy.

Contrary results are reported in two studies regarding the effect of *Ginkgo biloba* extracts on embryonic development (day 0-18 and 0-20, respectively). High dose administration of EGb 761 (HED: 1935 mg/kg per daily dose) caused no toxicity on maternal or fetal-placental data compared to low dose administration of a not specified *Ginkgo biloba* extract (HED: 417 and 535 mg/kg per daily dose) which caused high frequency (40-48%) of structural malformations. Another study supports harmful effects of ginkgo containing extracts on embryonic development. A low dose (HED: 68 and 135 mg/kg per daily dose) given from day 8-20 of pregnancy showed also toxic effects on embryonic development. Whereas no developmental toxic effects were found in a study from day 1-8 of pregnancy at low doses (HED: 33, 68, 135 mg/kg per daily dose).

Further, a protective effect of ginkgo containing extracts against chemotherapeutic-induced reproductive toxicity was observed.

In summary, a lot of pharmacological, pharmacokinetic and toxicological studies conducted with preparations of *Ginkgo biloba* leaf extract and its constituents exist. In considering the above-mentioned pharmacological data, clinical findings and derived indications for a well-established use can be supported by these studies. Pharmacokinetic studies of *Ginkgo biloba* leaf preparations and its constituents are available and give an evidence for numerical quantity values and bioavailability. Adequate toxicological data are mentioned, but for one, with no clinical relevance. As for these studies, which were performed, either no specific characterised extract was used or the applied doses were higher than the highest corresponding human dose of 120-240 mg or ginkgolic acids values were higher than those applied in clinical use, since the declaration of the *Ginkgo biloba* leaf extract in the Ph. Eur. states a maximum value of 5 ppm of ginkgolic acids.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

4.1.1.1. Primary pharmacodynamics

Effect on cognition

Geßner *et al.* (1985): In a double-blind trail 60 volunteers (57-77 years) with age-related mental deterioration participated to estimate the action of EGb 761 on the central nervous system. Quantitative pharmaco-electroencephalography (EEG) was used to assess the vigilance-promoting effects of the drug. Subjects were divided into three groups (n=20 in each group) and received randomly 3x40 mg/day EGb 761, 5 mg nicergoline or placebo. Analysis of the whole group for vigilance revealed no significant advantage of EGb 761 over the two reference substances. However, a subclassification of the subjects showed that the vigilance of those persons with a more unfavourable initial situation measured in the resting EEG could be clearly improved by chronic EGb 761 medication. This increase in vigilance was reflected at the behavioural level by an improvement of reaction times compared with the reference substances. These results show that chronic EGb 761 medication has a positive effect in geriatric subjects with deterioration of mental performance and vigilance, and this

effect is reflected at the behavioural level. In contrast, healthy subjects with a good initial state achieve hardly any improvement.

Elsabagh *et al.* (2005) conducted a placebo-controlled and double-blind study to compare the effects of LI 1370 after acute and chronic treatment on tests of attention, memory and executive function in 92 healthy subjects (18-26 years). Participants were randomly allocated to receive a single dose of LI 1370 (120 mg, n=26) or placebo (n=26). Another 40 were randomly allocated to receive LI 1370 (120 mg/day, n=20) or placebo (n=20) for a 6-week period. The acute dose of LI 1370 significantly improved performance on the sustained-attention task and patter-recognition memory task; however, there were no effects on working memory, planning, mental flexibility or mood. After 6 weeks of treatment, there were no significant effects of LI 1370 on mood or any of the cognitive tests. In conclusion, performance in tests of attention and memory was improved after acute administration of LI 1370. However, there were no effects after 6 weeks, indicating that tolerance develops to the effects in young, healthy subjects.

Santos *et al.* (2003) performed a double-blind, placebo-controlled study with 48 healthy men (60-70 years). Participants randomly received oral 80 mg/day dried *Ginkgo biloba* extract (produced by Maze Produtos Químicos e Farmaceuticos Ltda., 100 mg contained 24% flavonoide, 6.1% terpenoide, 2.7% bilobalide, 1.7% ginkgolide A, 0.9% ginkgolide B, and 0.8% ginkgolide C) or placebo for a period of 8 months. Evaluation of cognitive alterations was based on a number of neuropsychological tests including single photon emission computer tomography (SPECT) and measures of blood viscosity. The experimental group showed a reduction in blood viscosity, improved cerebral perfusion in specific areas and improved global cognitive functioning. In contrast, these parameters were opposite in the control group. These results suggest that *Ginkgo biloba* dry extract appears to be effective in the treatment of cognitive deficits in elderly.

Effect on blood flow

Guinot *et al.* (1989): An open study was conducted to examine the antagonistic activity of EGb 761 on PAF-induced platelet aggregation. 6 healthy volunteers received a single oral administration of 15 ml liquid extract (dose not indicated). Ex vivo platelet aggregation was determined by aggregometry on platelet-rich plasma. There was a reduction in platelet aggregation at all doses of PAF, as well as with 1 µM ADP and adrenaline. The most significant decreases occurred with 75 nM PAF 4 hours after intake ($p<0.05$) and 300 nM 4 ($p<0.01$) and 8 hours after intake ($p<0.05$). There were no concomitant changes in coagulation, skin bleeding time, haematological and biochemical laboratory tests, blood pressure or pulse. The results provide a possible explanation for the clinical efficacy of EGb 761 in the treatment of peripheral vascular disease.

Mehlsen *et al.* (2002) examined possible vasodilating effects of a *Ginkgo biloba* extract (Gibidyl Forte, produced in Denmark, containing 9.6 mg ginkgoflavonglycosides and 2.4 mg terpenlactones per tablet) on forearm haemodynamics. 16 healthy subjects with a median age of 32 years (range: 21-47) received three tablets daily of *Ginkgo biloba* or placebo. The study was performed in a randomised, double-blind, cross-over design for 6 weeks. Forearm blood flow was significantly higher during active treatment after 3 and 6 weeks as compared with placebo treatment for 3 and 6 weeks ($p<0.05$). Mean arterial blood pressure was unchanged, making the calculated FVR significantly lower during active treatment ($p<0.02$). It was concluded that oral treatment with a *Ginkgo biloba* extract (Gibidyl Forte) is able to dilate forearm blood vessels causing increments in regional blood flow without changing blood pressure levels in healthy subjects.

4.1.1.2. Secondary pharmacodynamics

No data available.

4.1.1.3. Safety pharmacology

No data available.

4.1.1.4. Pharmacodynamic interactions

Aruna and Naidu (2007): Coadministration of *Ginkgo biloba* (not further specified) at an oral dose of 120 or 240 mg, either with cilostazol or clopidogrel to 10 healthy male volunteers in a randomised, open-label, crossover study did not enhance antiplatelet activity. *Ginkgo biloba* potentiated the bleeding time prolongation effect of cilostazol. No significant correlation exists between prolongation of bleeding time and inhibition of platelet aggregation.

Wolf (2006) suggests that coadministration of aspirin and EGb 761 to 50 healthy male volunteers (20-44 years) in a double-blind, double-dummy study did not prolong coagulation parameters, including bleeding time and agonist-induced platelet aggregation, compared to aspirin alone. These results indicate that coadministration of the two drugs does not constitute a safety risk.

Jiang *et al.* (2005) analysed the effect of EGb 761 (80 mg three times daily) on clotting status and pharmacodynamics of warfarin in an open-label, three-way, crossover and randomised study. 12 healthy male subjects received a single 25 mg dose of warfarin alone or after 7 days pre-treatment with EGb 761. Dosing with *Ginkgo biloba* extract was continued for 7 days after warfarin administration. International normalised ratio of prothrombine time and platelet aggregation were not affected by *Ginkgo biloba* coadministration. Therefore, EGb 761 at recommended doses does not significantly affect clotting status or pharmacodynamics of warfarin in healthy subjects.

Jiang *et al.* (2006) investigated herb-drug interactions of *Ginkgo biloba* and warfarin. 24 healthy subjects received a single warfarin dose (25 mg) with or without pretreatment with Commission E recommended daily doses of EGb 761.The data were analysed using a population pharmacokinetic-pharmacodynamic modelling approach. *Ginkgo biloba* did not affect the pharmacokinetics or pharmacodynamics of S-warfarin in healthy subjects.

Duche *et al.* (1989) found that EGb 761 showed no effect on the hepatic microsomal drug oxidation system. 24 healthy male volunteers (19-35 years) in a randomised, double-blind study design received a single dose of 10 mg/kg antipyrine following a division in three groups and a treatment with 400 mg/day of EGb 761 (group 1), 300 mg/day phenytoin (group 2) or placebo (group 3). The elimination half-life of antipyrine was measured before and on the last day of the administration of the treatments. The results indicate that the half-life of antipyrine was not affected by EGb 761 and placebo treatment, whereas it was significantly decreased ($p<0.05$) from 12.2 to 6.8 hours after phenytoin control treatment.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

4.1.2.1. Absorption

The main pharmacokinetic parameters of the bioavailable terpene lactones after a single oral dose of 120 mg EGb 761 given either as tablets **(Kressman *et al.* 2002)** or as a solution **(cited in Biber 2003 from Fourtillan *et al.* 1995)** to 12 healthy volunteers are presented in table 1 and 2. The mean absolute bioavailability was 80% for ginkgolide A, 88% for ginkgolide B and 79% for biloalide given as a solution.

Table 1. Pharmacokinetic parameters of terpene lactones in 12 healthy volunteers after single oral administration of 120 mg EGb 761 **(Kressmann *et al.* 2002)**

	Ginkgolide A	**Ginkgolide B**	**Bilobalide**
C_{max} (ng/ml)	22.22 ± 4.57	8.27 ± 1.82	54.42 ± 13.62
t_{max} (h)	1.17 ± 0.39	1.54 ± 0.50	1.21 ± 0.45
$AUC_{0-\infty}$ (ng × h/ml)	121.35 ± 22.92	59.88 ± 11.39	217.24 ± 44.07
$T_{½}$ (h)	3.93 ± 0.40	6.04 ± 1.48	3.19 ± 0.40
Data are mean values ± SD			

Table 2. Pharmacokinetic parameters of terpene lactones in 12 healthy volunteers after single oral administration of 120 mg EGb 761 **(cited in Biber 2003 from Fourtillan *et al.* 1995)**

	Ginkgolide A	**Ginkgolide B**	**Bilobalide**
C_{max} (ng/ml)	33.29 ± 9.12	16.46 ± 5.02	18.81 ± 8.84
t_{max} (h)	1.06 ± 0.72	1.17 ± 0.69	1.17 ± 0.80
$AUC_{0-\infty}$ (ng × h/ml)	146 ± 21.50	109.90 ± 20.60	78.97 ± 38.98
$T_{½}$ (h)	4.50 ± 1.55	10.57 ± 3.56	3.21 ± 0.64
Data are mean values ± SD			

According to **Fourtillan *et al.* (1995)** food intake did not modify bioavailability of ginkgolides A, B and bilobalide, although their rate of absorption was slowed, as revealed by a delayed T_{max}.

Biber (2003): In a dose-response study, 12 healthy volunteers received 80, 120 and 240 mg EGb 761 as a solution. The results are shown in table 3.

Table 3. Pharmacokinetic parameters after oral administration of EGb 761 in healthy volunteers **(Biber 2003)**

Extract dose (mg)	**Constituent dose (mg)**	**C_{max} (ng/ml)**	**T_{max} (h)**	**AUC (ng × h/ml)**	**$T_{½}$ (h)**
Ginkgolide A					
80	1.056	15.2 ± 2.8	0.61 ± 0.21	69.9 ± 18.4	4.5 ± 2.5
120	1.584	25.3 ± 9.9	0.60 ± 0.20	103.2 ± 16.3	4.5 ± 1.6
240	3.168	42.9 ± 9.1	0.75 ± 0.20	211.1 ± 37.6	5.1 ± 1.4
Ginkgolide B					
80	0.560	6.53 ± 1.23	1.29 ± 0.62	43.75 ± 8.77	6.5 ± 2.6
120	0.840	9.12 ± 1.48	0.92 ± 0.25	70.03 ± 19.55	8.5 ± 3.0
240	1.680	18.11 ± 4.16	1.21 ± 0.32	140.69 ± 33.62	9.9 ± 2.0
Bilobalide					
80	2.280	30.2 ± 12.6	0.86 ± 0.40	114.7 ± 56.7	5.5 ± 3.6
120	3.420	35.2 ± 8.3	0.67 ± 0.18	128.1 ± 58.4	4.0 ± 1.7
240	6.840	58.6 ± 19.1	0.72 ± 0.20	247.1 ± 107.1	4.9 ± 2.5

As reported in the German monograph of the Commission E, the absolute oral bioavailability was 98-100% for ginkgolide A, 79-93% for ginkgolide B and > 70% for bilobalide after oral administration of EGb 761 **(Commission E monograph on *Ginkgo biloba* leaf dry extract, 1994)**.

Chan *et al.* (2007): After an oral dose of EGb 761 (80 mg) maximum plasma levels of ginkgolide A (C_{max}=15 ng/ml) and ginkgolide B (C_{max}=4 ng/ml) were attained at 1.4-2.0 hours. The half-lives of ginkgolide A and ginkgolide B were 3.9 and 7 hours.

Woelkart *et al.* (2010) investigated bioavailability and pharmacokinetics of ginkgo terpene lactones of three different *Ginkgo biloba* L. preparations; ginkgo fresh plant tincture, where 1 ml contains the equivalent of 920 mg *Ginkgo biloba* leaves as active ingredient (ethanol for extraction, DER=1:9), one new ginkgo fresh plant extract tablet (250 mg) comprises 90 mg of ginkgo fresh plant extract (ethanol for extraction, DER=3-5:1) and EGb 761 tablets (40 mg). The study was conducted in a randomised, open, parallel group design with 24 healthy volunteers. Subjects received a single oral dose of the different formulations with diverse amounts of terpene trilactones. The applied oral doses were the corresponding maximum registered daily dose, which is 2512 mg of the tincture, 1000 mg of the fresh plant extract tabvlets and 120 mg for EGb 761. The results demonstrate relative bioavailability of different *Ginkgo biloba* L. preparations.

Table 4. Maximum concentrations (median) of terpene lactones in plasma after administration of the maximum daily dose of different ginkgo preparations **(Woelkart *et al.* 2010)**

	Ginkgo plant fresh tincture	**Ginkgo fresh plant extract tablet**	**EGb 761**
C_{max} (ng/ml)			
Bilobalide	3.53	11.68	26.85
Ginkgolide A	3.62	7.36	16.44
Ginkgolide B	1.38	4.18	9.99

Wójcicki *et al.* (1995): The following table shows pharmacokinetic parameters of the flavonol glycosides quercetin, kaempferol and isorhamnetin after a single administration of EGb 761 (no dose mentioned) in three different formulations in an equal amount given to 18 volunteers.

Table 5. Pharmacokinetic parameters of flavonol glycosides after a single oral dose of EGb 761 to healthy subjects **(Wójcicki *et al.* 1995)**

	Capsules	**Drops**	**Tablets**
Quercetin			
C_{max} (ng/ml)	12.16 ± 0.60	13.79 ± 0.77	13.45 ± 0.74
t_{max} (h)	2.47 ± 0.05	2.00 ± 0.07	2.00 ± 0.08
$AUC_{0-24\,h}$ (ng × h/ml)	63.71 ± 2.99	64.66 ± 3.62	60.15 ± 3.46
Kaempferol			
C_{max} (ng/ml)	26.73 ± 1.19	30.02 ± 1.28	28.94 ± 1.24
t_{max} (h)	2.44 ± 0.06	2.03 ± 0.08	2.03 ± 0.08
$AUC_{0-24\,h}$ (ng × h/ml)	138.43 ± 6.69	138.08 ± 7.08	130.37 ± 6.92
Isorhamnetin			
C_{max} (ng/ml)	7.26 ± 0.37	9.62 ± 1.61	7.81 ± 0.31
t_{max} (h)	2.44 ± 0.07	2.03 ± 0.08	2.03 ± 0.08
$AUC_{0-24\,h}$ (ng × h/ml)	34.63 ± 1.99	39.99 ± 6.13	31.55 ± 1.89
Data are mean values ± SE			

4.1.2.2. Distribution

No data available.

4.1.2.3. Metabolism

Chang *et al.* (2006): In the following *in vitro* study the effect of *Ginkgo biloba* extract constituents on procarcinogen-bioactivating human CYP1 enzymes was investigated. It was shown that the aglycones of quercetin, kaempferol, and isorhamnetin inhibited CYP1B1, CYP1A1, and CYP1A2. The most potent inhibitor of CYP1B1 was isorhamnetin with a K_i-value of 3±0.1 nM, whereas quercetin was with K_i=418±50 nM the least potent inhibitor of CYP1A2. *Ginkgo biloba* extract also reduced benzo[a]pyrene hydroxylation, and the effect was greater with CYP1B1 than with CYP1A1 as the catalyst. In summary, these novel findings from the present study indicate that *Ginkgo biloba* extract and the flavonol aglycones, isorhamnetin, kaempferol, and quercetin, preferentially inhibit the *in vitro* catalytic activity of human CYP1B1.

4.1.2.4. Elimination

No data available.

4.1.2.5. Pharmacokinetic interactions with other medicinal products

Studies with defined *Ginkgo biloba* extract (EGb 761)

Robertson *et al.* (2008): Evaluation of an open-label study in 14 healthy volunteers showed that lopinavir, ritonavir and fexofenadine (probe drug for P-gp) exposures were not significantly affected by *Ginkgo biloba* (according to an internet research the used extract is probably EGb 761) administration of 120 mg twice daily for 2 weeks. However, *Ginkgo biloba* decreased midazolam (probe drug for CYP3A4) $AUC_{0-\infty}$ and C_{max} by 34% (p=0.03) and 31% (p=0.03), respectively, relative to baseline.

Uchida *et al.* (2006): This study was performed to demonstrate the influence of repeated oral administration of EGb 761 (120 mg three times daily for 28 days) on CYP2C9 and CYP3A4. CYP2C9 probe (tolbutamide, 125 mg) and CYP3A4 probe (midazolam, 8 mg) were orally administered to 10 male healthy volunteers (mean age ± SD: 24.9 ± 2.6 years) before and after EGb 761 intake, and they received 75 g glucose after tolbutamide administration. $AUC_{0-\infty}$ for tolbutamide after EGb 761 intake was slightly but significantly (16%) lower than that before EGb 761 intake. Concomitantly, EGb 761 tended to attenuate AUC_{0-2} of blood glucose-lowering effect of tolbutamide. $AUC_{0-\infty}$ for midazolam was significantly (25%) increased by EGb 761 intake and oral clearance was significantly (26%) decreased.

Markowitz *et al.* (2003) assessed in normal volunteers (n=12) aged 22-40 years the influence of EGb 761 on the activity of CYP2D6 and 3A4 normal volunteers phenotyped as CYP2D6 extensive metabolisers. Probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were coadministered orally at baseline, and following treatment with EGb 761(120 mg twice daily) for 14 days. Urinary concentrations of dextromethorphan and dextrorphan were quantified and dextromethorphan metabolic ratios (DMRs) were determined at baseline and after EGb 761 treatment. Likewise, plasma samples were collected (0-60 hours) for alprazolam pharmacokinetics at baseline and after EGb 761 treatment to assess effects on CYP3A4 activity. Validated HPLC methods were used to quantify all compounds and relevant metabolites. No statistically significant differences were found between baseline and post-EGb 761 treatment DMRs indicating a lack of effect on CYP2D6. For alprazolam there was a 17% decrease in the area under the plasma concentration versus time curve (AUC); (p<0.05). However, the half-life of elimination was not significantly different after EGb 761 administration indicating a lack of hepatic CYP3A4 induction. The usual interpretation of altered C_{max} and no variation in the half-life of elimination is that absorption rather than hepatic enzyme activity has been affected.

Greenblatt *et al.* (2006): The study shows that short-term exposure to EGb 761 in a dosage of 360 mg per day does not influence the kinetics of CYP2C9 activity. 11 healthy volunteers received single 100 mg doses of flurbiprofen, a probe substrate for CYP2C9, and EGb 761 or placebo in a randomised, double-blind, 2-way crossover study. None of the mean kinetic variables differences for flurbiprofen with either placebo or EGb 761 were significant. Based on HPLC analysis, each 60 mg ginkgo tablet contained 6.6 µg of amentoflavone and 61.2 µg of quercetin, both previously identified as CYP2C9 inhibitors. These amounts were apparently too low to inhibit CYP2C9 function *in vivo*. These results confirm previous controlled clinical studies showing no effect of ginkgo on the kinetics of warfarin, which is known as a substrate of CYP2C.

Zadoyan *et al.* (2011): The objective of this open-label, single-center, randomised, threefold cross-over study was to assess the *in vivo* herbal drug-drug interaction potential of EGb 761 with respect to the activities of the five major human drug-metabolising cytochrome P450 (CYP) enzymes. 18 healthy volunteers received in random order placebo twice daily, EGb 761 120 mg twice daily, and EGb 761 240 mg in the morning and placebo in the evening for 8 days. After the mentioned pretreatment, on day 8, administration was performed together with the orally administered phenotyping cocktail: 150 mg caffeine, 125 mg of tolbutamide, 20 mg omeprazole, 30 mg dextromethorphan, and 2 mg of midazolam. No relevant pharmacokinetic interaction was assumed if the 90% CIs for EGb 761/placebo ratios of pharmacokinetic parameters were within the 0.70-1.43 range. The results show respective CIs were within the specified margins for all ratios except CYP2C19 for EGb 761 120 mg twice daily (90% CI 0.681-1.122) and for CYP2D6 for EGb 761 240 mg once daily (90% CI 0.667-1.281). These findings were attributed to the intraindividual variability of the metrics used. In conclusion, EGb 761 has no relevant effect on the *in vivo* activity of the major CYP enzymes in humans and therefore has no relevant potential to cause respective metabolic drug-drug interactions.

Blonk *et al.* (2012) studied the effect of EGb 761 on the pharmacokinetics of raltegravir in an open-lable, randomised, two-period, crossover phase I trial in 18 healthy volunteers between the ages of 18 and 55 years. Subjects received 120 mg EGb 761 twice daily for 15 days plus a single dose of raltegravir (400 mg) on day 15, a washout period, and 400 mg of raltegravir on day 36 or the test and reference treatments in reverse order. Pharmacokinetic sampling of raltegravir was performed up to 12 hours after intake on an empty stomach. All subjects completed the trial, and no serious adverse events were reported. Steady-state EGb 761 increased the mean exposure to raltegravir ($AUC_{0-\infty}$) by 21% and the C_{max} by 44%. The apparent elimination half-life of raltegravir did not appear to be influenced by EGb 761. Geometric mean ratios (90% CI) of the area under the plasma concentration-time curve from dosing to infinity ($AUC_{0-\infty}$) and the maximum plasma concentration (C_{max}) of raltegravir with EGb 761 versus raltegravir alone were 1.21 (0.93 to 1.58) and 1.44 (1.03 to 2.02). Besides EGb 761 did not reduce raltegravir exposure, the observed increase in C_{max} may be caused by a change in absorption than by inhibition of the metabolim of raltegravir, because the elimination half-life of raltegravir remained unaffected. At which the increase in C_{max} is not considered to be of clinical importance. A possible explanation for the increase in the C_{max} and bioavailability of raltegravir when combined with EGb 761 could be the inhibition of P-gp by EGb 761. Although i*n vitro* characterisation of raltegravir transport by drug transporters indicates that raltegravir is a weak P-gp substrate, one must be cautious because it is not yet confirmed in human studies.

In the article by **Zagermann-Muncke (2006)** the role of transport proteins in view of pharmacokinetic interactions is discussed. The ABC transporter P-gp can be both inhibited and induced, whereas P-gp substrates are usual substrates of CYP3A4 as well. Expression and activity of both proteins are apparently regulated in part through the same menchanisms. Thereby differentiation of effects is hindered. A list of P-gp substrates, inducers and inhibitors is given. The concomitant intake of a P-gp substrate and a P-gp inhibitor is possibly leading to a higher bioavailability of the P-gp substrate. This could be clinically relevant for drugs with narrow therapeutic index. Genetically based

MDR-1 (gene that encodes for P-gp) polymorphism can change transport function and expression of P-gp, therefore efficacy and tolerance of drugs, which are P-gp substrates, can vary between humans.

Jiang *et al.* (2005) analysed the effect of EGb 761 (80 mg three times daily) on pharmacokinetics of warfarin in an open-label, three-way, crossover and randomised study. 12 healthy male subjects received a single 25 mg dose of warfarin alone or after 7 days pre-treatment with EGb 761. Dosing with *Ginkgo biloba* extract was continued for 7 days after warfarin administration. There was no relevant influence on the apparent clearance of S- and R-warfarin. EGb 761 did not affect the apparent volumes of distribution or protein binding of either S-warfarin or R-warfarin. Therefore, EGb 761 at recommended doses does not significantly affect the pharmacokinetics of warfarin in healthy subjects.

Lu *et al.* (2006): To examine whether ticlopidine coadministration with EGb 761 would affect pharmacokinetics of ticlopidine 8 healthy volunteers were included in a sequential 3-phase study. Subjects were treated with a single oral dose of 250 mg ticlopidine alone or after pretreatment with EGb 761 (40 mg 3 times daily) for 4 days. Ticlopidine and EGb 761 significantly inhibited the organic anion transporting polypeptide (OATP-B)-mediated uptake of [^{3}H]-estrone-3-sulfate in a concentration-dependent manner. When EGb 761 is coadministered with ticlopidine there were no changes in the pharmacokinetic parameters of ticlopidine.

Kudolo *et al.* (2006): A study is described which was designed as a double-blind, placebo-controlled, crossover trial to determine if the coingestion of EGb 761 and metformin would alter the pharmacokinetic properties of metformin in type 2 diabetic patients and in non-diabetic persons. The participants ingested either EGb 761 (120 mg/day as a single dose) or placebo for 3 months. At the end of the period the non-diabetic persons took a single 500 mg dose of metformin and the diabetic subjects took his/her prescribed metformin dose (250-850 mg) with 120 mg EGb 761.The pharmacokinetic parameters of metformin (500 mg) were all significantly different ($p<0.05$) between the normal glucose tolerance and 8 out of 10 diabetic subjects who received metformin during the placebo cycles. During the EGb 761 cycles, only the elimination half-life in the type 2 diabetic patients was significantly increased. In conclusion, coingestion of 120 mg EGb 761 and 500 mg metformin did not significantly affect the pharmacokinetic properties of metformin.

Gardner *et al.* (2007): The purpose of this randomised, double-blind, placebo-controlled, parallel clinical trial was to determine potential adverse effects of concomitant intake of aspirin and EGb 761 on platelet function. EGb 761 (300 mg/day) was compared with placebo for effects on measures of platelet aggregation among adults (69±10 years) consuming 325 mg/day aspirin. Participants were afflicted with peripheral artery disease (PAD) or had risk factors for cardiovascular disease. Outcome measures included platelet function analysis (PAF-100 analyser) using ADP as agonist, and platelet aggregation using ADP, epinephrine, collagen and ristocetin as agonists. There were no clinically or statistically significant differences between treatment groups for any agonists, for either PAF-100 analysis or platelet aggregation. In conclusion, in older adults with PAD or cardiovascular disease risk, a relatively high dose of EGb 761 combined with 325 mg/day daily aspirin did not have a clinically or statistically detectable impact on indices of coagulation examined over 4 weeks, compared with the effect of aspirin alone. No adverse bleeding events were observed.

Studies with other *Ginkgo biloba* extracts

Bressler (2005) presented in a review article “known drug interactions with *Ginkgo biloba*” (not further specified). In a table interactions with the following prescription drugs are listed: alprazolam, haloperidol, trazodone, omeprazole, aspirin, ibuprofen, nifedipine and warfarin. To specify these interactions, systemic exposure to alprazolam may be slightly decreased by *Ginkgo biloba*. *Ginkgo biloba* can increase the effectiveness and decrease the extrapyramidal side effects of haloperidol and can increase the risk of sedation when taken together with trazodone. Plasma concentrations of

omeprazole may be reduced when the medicinal product is taken together with *Ginkgo biloba* which can result in decreased efficacy of the drug. Administration of Nifedipine and *Ginkgo biloba* at once may elevate plasma concentrations of the cardiovascular agent. Based on the suspected mechanism of action that *Ginkgo biloba* can also inhibit CYP3A4, it may causes increased levels of drug, prolonged drug effects, and increased drug toxicity. The risk of bleeding may be increased when *Ginkgo biloba* is administered concomitantly with aspirin, ibuprofen or warfarin.

Mahadevan and Park (2008) mentioned with references to the primary literature interactions of *Ginkgo biloba* extract with the following substances: antidepressants (i.e. trazodone), antiepileptics, antidiabetics, diuretics, and nonsteroidal anti-inflammatory drugs, as well as other herbal drugs. These interactions are believed to be affected mainly by flavonol glycosides and the terpene lactones by selectively inhibiting particular enzymes, including cytochrome P450. However, others reported no effect on clearance of cytochrome P450 substrates by ginkgo leaf extract.

Yoshioka *et al.* (2004b): The effects of *Ginkgo biloba* leaf extract (manufactured in Chiba, Japan) on the pharmacokinetics of nifedipine (NFP), a calcium-channel blocker, were studied using 8 healthy volunteers. Concomitant oral administration of *Ginkgo biloba* (240 mg) did not significantly affect any of the mean pharmacokinetic parameters of either NFP or dehydronifedipine, a major metabolite of NFP after oral intake of 10 mg NFP. Still, the C_{max} of NFP in 2 subjects was approximately doubled by GBE, and they had severer and longer-lasting headaches with *Ginkgo biloba* than without *Ginkgo biloba*, with dizziness or hot flushes in combination with *Ginkgo biloba* extract. In addition the mean heart rate after oral administration of NFP with ginkgo extract tended to be faster than that without *Ginkgo biloba* extract at every time point. In conclusion, *Ginkgo biloba* extract and NFP should not be simultaneously ingested as much as possible and careful monitoring is needed when administering NFP concomitantly with *Ginkgo biloba* to humans.

Fan *et al.* (2009a): The aim of the present study was to assess the effects of *Ginkgo biloba* extract (not further specified) on the pharmacokinetics of talinolol, a P-glycoprotein substrate. 12 healthy male volunteers took a single 100 mg oral dose of talinolol either alone (control group) or after pre-treatment with 120 mg *Ginkgo biloba* extract three times daily for 14 days. *Ginkgo biloba* extract treatment considerably increased talinolol AUC_{0-24} and C_{max} by 21% (p=0.002) and 33% (p=0.002), respectively, whereas $t_{½}$ and t_{max} indicated no alteration. The results suggest that *Ginkgo biloba* extract significantly inhibited P-glycoprotein in humans.

Fan *et al.* (2009b) investigated the effects of single and repeated *Ginkgo biloba* extract ingestion on the oral pharmacokinetics of talinolol. Ten healthy male volunteers participated in a 3-stage sequential study. Plasma concentrations of talinolol were measured by HPLC after talinolol 100 mg was administered alone, with a single oral dose of *Ginkgo biloba* extract (120 mg), and after 14 days of repeated *Ginkgo biloba* extract ingestion (360 mg/day). A single oral dose of GBE did not affect the pharmacokinetics of talinolol. Repeated ingestion of *Ginkgo biloba* extract significantly increased C_{max} (36%), AUC_{0-24} (26%) and $AUC_{0-\infty}$ (22%) of talinolol without significant changes in elimination half-life and the time to C_{max}. These results indicate that long-term use of *Ginkgo biloba* extract significantly influence talinolol disposition in humans, likely by affecting the activity of P-glycoprotein inhibition and/or other drug transporters.

Yin *et al.* (2004) designed this study to investigate the potential herb-drug interaction between *Ginkgo biloba* leaf extract (containing 22.9% flavonol glycosides and 6.8% terpene lactones) and omeprazole, a widely used CYP2C19 substrate. 18 healthy Chinese subjects with different CYP2C19 genotypes received a single omeprazole 40 mg at baseline and then at the end of a 12-day treatment period with *Ginkgo biloba* leaf extract (140 mg, 2 times daily). The resulting pharmacokinetic parameters of omeprazole, and its metabolites, 5-hydroxyomeprazole and omrprazole sulfone, show that *Ginkgo biloba* leaf extract can induce omeprazole hydroxylation in a CYP2C19 genotype-dependent

manner and concurrently reduce the renal clearance of 5-hydroxyomeprazole. In conclusion, coadministration of *Ginkgo biloba* with omeprazole or other CYP2C19 substrates may significantly reduce their effect.

Kim *et al.* (2010) evaluated the potential pharmacokinetic interactions between ticlopidine and *Ginkgo biloba* extract (not further specified). 24 healthy Korean male volunteers (24±4.3 years) participated in this open-label, randomised, 2-period, 2-treatment, 2-sequence, single- dose, crossover study. All volunteers were randomly assigned to a sequence group for the 2 treatment, separated by a 1-week washout period between the treatments. Group 1 received ticlopidine 250 mg alone and group 2 ticlopidine 250 mg with *Ginkgo biloba* extract 80 mg. Concentrations of ticlopidine were determined by using HPLC and ultraviolet detection. The geometric mean ratios of the ticlopidine/ginkgo group to the ticlopidine test group were 1.03 for C_{max}, 1.08 for $AUC_{0\text{-}last}$, and 1.10 for $AUC_{0\text{-}\infty}$. In conclusion, coadministration of *Ginkgo biloba* extract and ticlopidine was not associatetd with any significant changes in the pharmacokinetic profile of ticlopidine compared with ticlopidine administered alone.

Mauro *et al.* (2003): An open label, randomised, crossover investigation was conducted in 8 healthy volunteers aged 20-28 years to determine the effect of *Ginkgo biloba* leaf extract (containing 24% flavone glycosides and 6% terpene lactones, ethanolic extracting solvent, 80 mg three times daily) on digoxin (0.5 mg) pharmacokinetics. No significant difference between treatments was observed with respect to $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, Cl, $t_{½}$ and k_e of digoxin. In conclusion, the concomitant use of *Ginkgo biloba* leaf extract and digoxin did not appear to have any significant influence on the pharmacokinetics of orally administered digoxin in healthy volunteers.

Lei *et al.* (2009a): To assess the effect of *Ginkgo biloba* extract (manufactured by Now Foods, Bloomingdale, IL, USA) on the pharmacokinetics of bupropion 14 healthy male volunteers ingested a single oral dose of 150 mg bupropion alone and during treatment with *Ginkgo biloba* extract 240 mg/day (two 60 mg capsules taken twice daily) for 14 days. *Ginkgo biloba* extract administration resulted in no statistically significant effect on the pharmacokinetic parameters of bupropion.

Lei *et al.* (2009b): The following study was performed to examine the effect of concurrent administration of *Ginkgo biloba* (manufactured by Now Foods, Bloomingdale, IL, USA) on the single-dose pharmacokinetics of voriconazole in Chinese volunteers genotyped as either CYP2C19 extensive or poor metabolisers. In a randomised, 2-phase crossover design 14 healthy volunteers received a single 200 mg oral dose of voriconazole without pretreatment (control) and after pretreatment with 120 mg of *Ginkgo biloba* capsules twice daily for 12 days. In between of the study phases there was a 4-week washout period. The results show that administration of *Ginkgo biloba* 120 mg twice daily for 12 days to CYP2C19 extensive metabolisers and poor metabolisers had no statistically significant effect on the pharmacokinetics of single-dose voriconazole. Therefore, the pharmacokinetic interactions between voriconazole and *Ginkgo biloba* may have limited clinical significance.

Zuo *et al.* (2010): The objective of the following study was to assess the possible pharmacokinetic interaction between *Ginkgo biloba* extract (composed of 24% flavone glycosides and 6% terpene lactones, manufactured in China) and diazepam, when administered simultaneously to 12 Chinese healthy male subjects. The pharmacokinetic parameters of diazepam and one of its metabolites, N-demethyldiazepam, were compared after oral administration of diazepam (10 mg) in the absence or presence of oral *Ginkgo biloba* extract (120 mg 2 times daily) for 28 days. The 90 % CIs of the ratios of mean pharmacokinetic parameters of diazepam presence and absence of *Ginkgo biloba* extract were well within the 80-125% bioequivalence range. These results suggest that *Ginkgo biloba* extract, when taken in normally recommended doses over a 4-week time period, may not affect the pharmacokinetics of diazepam via CYP2C19 and the excretion of N-desmethyldiazepam in healthy volunteers. There was also no drug-drug interaction observed between *Ginkgo biloba* and diazepam.

Mohutsky *et al.* (2006) conducted two open-label, crossover pharmacokinetic studies in healthy volunteers to determine the effect of *Ginkgo biloba* extract (Ginkgold, Nature's Way, Springville, UT) on 2 probe substrates of CYP2C9, diclofenac and tolbutamide. Diclofenac study: Diclofenac potassium 50 mg (immediate release) was administered to 12 subjects twice daily for 14 days. Gingko biloba extract tablets, 120 mg twice daily, were given concurrently on days 8-15. Tolbutamide study: Tolbutamide was administered as single 500 mg oral dose to 6 subjects. After a minimum of a 2-week washout period, the subjects started *Ginkgo biloba* treatment phase consisting of 120 mg *Ginkgo biloba* extract twice daily for 3 days. On day 4, the patients received a second 500 mg dose of tolbutamide. No interactions between *Ginkgo biloba* extract and CYP2C9 probe substrates were observed *in vivo* as evidenced by the lack of effect on the steady-state pharmacokinetics of diclofenac or on the urinary metabolic ratio of tolbutamide.

Gurley *et al.* (2005) noted no effect of *Ginkgo biloba* on cytochrome P450 activity in this open-label study. The aim of this study was to determine whether long-term supplementation, beside others, of *Ginkgo biloba* (60 mg four times daily standardised to 24% flavone glycosides and 6% terpene lactones) affected cytochrome P450 activity. 12 healthy volunteers (60-76 years) were randomly assigned to receive each botanical supplement for 28 days followed by a 30-day washout period. Probe drug cocktails of 8 mg midazolam, 100 mg caffeine, 500 mg chlorzoxazone and 5 mg debrisoquine were administered before and at the end of supplementation. Pre- and post-supplementation phenotypic ratios were determined for CYP3A4, CYP1A2, CYP2E1 and CYP2D6. Comparisons of pre- and post-*Ginkgo biloba* phenotypic ratios revealed no significant changes in the CYP activity tested in this study.

Yasui-Furukori *et al.* (2004) designed the study to examine the effect of *Ginkgo biloba* extract (manufactured in Ichoha Sainoshin, Aihoupu Co., Kagoshima, Japan) on the pharmacokinetics of donepezil in 14 elderly patients with Alzheimer's disease. Subjects received donepezil 5 mg/day, supplemented with *Ginkgo biloba* extract 90 mg/day for 30 days. Plasma drug concentration was measured using HPLC. The resulting plasma concentration of donepezil during GBE supplementation (mean±SD [95% CI]; 24.4±12.6 ng/ml [17.1-31.7 ng/ml]) was not significantly different from that before ginkgo supplementation (22.7±10.3 ng/ml [16.8-28.7 ng/ml]) or that 4 weeks after its discontinuation (25.0±12.9 ng/ml [17.6-32.4 ng/ml]). In conclusion, the results show that ginkgo supplementation does not have major impact on the pharmacokinetics of donepezil.

4.2. Clinical Efficacy

4.2.1. Dose response studies

4.2.2. Clinical studies (case studies and clinical trials)

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
Herrschaft *et al.* 2012	24 weeks randomised, double-blind, placebo-controlled	EGb 761 (240 mg once daily) or placebo	n=410 n=205 verum n=205 placebo ≥50 years	mild to moderate AD or VaD associated with neuropsychiatric symptoms	changes in the SKT and NPI total score	improvement of 2.2±3.5 points on the SKT in the EGb 761 group and 0.3±3.7 points on placebo, NPI score improved by 4.6±7.1 in the EGb 761 group and by 2.1±6.5 in the placebo group, both drug-placebo comparisons were significant at p<0.001	119 AE in 91 (44.4%) EGb 761 treated patients and 126 AEs for 82 patients (40.0%) of the placebo group; no major differences, except for dizziness with 7.3% in the placebo group and 2.0% in the EGb 761 group; three serious AE in the EGb 761 group were judged unrelated to the trial medication
Ihl *et al.* 2010a	24 weeks randomised, double-blind, placebo-controlled, parallel	EGb 761 (240 mg once daily) or placebo	n=404 n=202 verum n=202 placebo ≥50 years	Mild to moderate dementia with neuropsychiatric features, at least 50 years, probable AD in accordance with the NINCDS-ADRA criteria, possible AD with cerebrovascular disease (CVD) as	change of the SKT total score (cognitive efficacy) and the 12-item NPI total score (neuropsychiatric efficacy) during trial period	improvement of SKT score in 32% in the EGb 761 group and in 15% in the placebo group, improvement of NPI total score in 45%in the EGb 761 group and 24% in placebo group, significant superiority of	no difference of incidence of AE in the treatment groups; seven times more patients with tinnitus in the placebo group; dizziness: 19 (9.2%) in EGb 761 group and 23 (11.3%) in placebo group; serious AE:

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
				defined by the NINDS-AIREN criteria or probable VaD according to NINDS-AIREN, symptoms of dementia at least for 6 months, CT or MRI scan no more than 1 year old, consistent with the inclusion diagnosis and showing no evidence of other brain lesions that could account for the cognitive deficit		EGb 761 over placebo in both primary endpoints (p<0.001)	EGb 761 group (ischaemic stroke and stage IV lung cancer), placebo group (ischaemic stroke and rapid deteriora-tion of intellectual and motor function)
Napryeyenko and Borzenko 2007	22 weeks randomised, double-blind, placebo-controlled, parallel	EGb 761 (120 mg twice daily) or placebo	n=391 n=196 verum n=195 placebo ≥50 years	mild to moderate dementia with neuropsychiatric features; ≥50 years, probable AD (NINCDS-ADRDA), possible AD (NINCDS/ADRDA), with CVD (NINDS-	SKT	mean -3.2-point improvement in the SKT on EGb 761 and average deterioration by +1.3 points on placebo (p<0.001); EGb 761 was significantly superior to placebo with respect to	EGb 761 group: 166 patients reported 302 AE, placebo group: 178 patients reported 481 AE; dizziness: 12 (6%) in EGb 761 group and 36 (18%) in placebo group; 7 non-fatal serious AE were

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
				AIREN), probable VaD (NINDS-AIREN), CT or MRI scan no more than one year old, no other brain lesions, TE4D score below 36, SKT score from 9 to 23, CDT score below 6, score at least 5 on the 12-item NPI with at least one item score being 3 or higher, score below 20 on the 17-item HAMD, presence of caregiver		all (primary and secondary)efficacy variables ($p<0.001$)	reported on EGb 761 and 13 on placebo; no event of bleeding
Yancheva *et al.* 2009	22 weeks randomised, double-blind, donepezil-controlled, parallel	EGb 761 (120 mg twice daily), or donepizil (5 mg once daily during first 4 weeks,	n=96 n=30 verum n=29 control n=29 verum +control	AD and neuropsychiatric features, meet NINCDS/ADRAD criteria, score below 36 on the TE4D, below 6 on the Clock-Drawing Test (CDT),	no primary outcome measures were defined, outcome of interest were the SKT, the CDT and the Verbal Fluency Test (cognitive domain), the NPI	improvement in all tests and rating scales in all groups, no statistically significant differences, relatively consistent but not significant, slight superiority of the	AE in 32% of EGb 761 group, 73% in donepezil group and 56% in combined treatment group; fewer AE (related to study medication) in EGb 761 group than in the other

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
		10 mg during last 18 weeks), or combined treatment (at recom-mended doses)	≥50 years	between 9 and 23 on the SKT, at least score five on the 12-item NPI	and the HAMD (behavioural and psychological domain), the GBS (overall geriatric assessment)	combined treatment over the single drugs	groups (p=0.01); most frequent: headache, insomnia, diarrhoea, and fatigue
Kanowski *et al.* 1996	24 weeks randomised, double-blind, placebo controlled, parallel	EGb 761 (120 mg twice daily) or placebo	n=156 n=79 verum n=77 placebo ≥55 years	mild to moderate primary degenerative dementia of the AH type or multi-infarct dementia (MID); SKT score between 6-18 (inclusive), MMSE score between 13-25 (inclusive)	psychopathological assessment (CGI), cognitive performance assessment (SKT), assessment of behaviour (NAB), clinical efficacy assessment (therapy response defined as response in at least two of the three primary variables-Fisher's Exact Test)	responder rates in CGI and SKT higher under EGb 761 compared to placebo (p<0.05), in NAB tendency in favour of EGb 761 (p<0.1), frequency of therapy responders differed significantly in favour of EGb 761 (p<0.005) in Fisher's Exact Test	122 AE, 63 AE on EGb 761 and 59 on placebo; gastro-intestinal disorders occurred more frequently and in higher intensity on placebo; 7 serious AE (5 on EGb 761 and 2 on placebo), one serious AE "suspected acute cerebral incident" was related to study drug (investigator declined to comment)

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
Heinen-Kammerer *et al.* 2005	12 months non-randomised, two-armed, open, standard-controlled, parallel	EGb 761 (no dose mentioned) or standard (no *Ginkgo biloba* extract, previous standard therapy could be continued)	n=683 n=281 verum n=402 standard 65-80 years	mild to moderate dementia; MMSE score between 12 and 24, 65-80 years, family member as caregiver at home, speak German, no aphasia, signed informed consent	quality of life of care-taking relatives and patients on the basis of PLC (quality of life profile of chronically ill patients)	according to PLC a significant improvement in quality-of-life of care taking relatives ($p<0.001$) and patients (positive mood $p=0.018$, negative mood $p<0.001$) was observed in the ginkgo group	14 inpatient stays (5 on EGb 761, 9 on standard) causally determined to dementia
Le Bars *et al.* 1997	52 weeks randomised, double-blind, placebo controlled, parallel	EGb 761 (40 mg three times daily) or placebo	n=309 n=155 verum n=154 placebo ≥45 years	mildly to severely demented patients with AD or multi-infarct dementia, without other significant medical conditions	changes in cognitive impairment (ADAS-Cog), in daily living and social behaviour (GERRI), and in general psychopathology (CGIC)	50% of EGb 761 group completed the study and 38% of placebo group; no significant change in the ADAS-Cog for EGb 761 group, a significant worsening of 1.5 points ($p=0.006$) on placebo; mild improvement in the GERRI on EGb 761, significant worsening on	5 serious AE not related to the study medication; 188 AE, 97 on EGb 761 and 91 on placebo, majority mild to moderate intensity (167/188); AE of severe intensity (12 for EGb 761 and 9 for placebo) resulted in withdrawal in 2 patients on EGb 761 and 1 on

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
						placebo (0.08 points; p=0.02), statistically significant difference in favour of EGb 761 (p=0.004); slight worsening for both treatment groups on the CGIC; AD subgroup analysis: similar results for both treatments, differences were significant on ADAS-Cog (p=0.02) and GERRI (p<0.001)	placebo; gastrointestinal events more often on EGb 761 (18 of 29 events)
Hofferberth 1989	8 weeks randomised, double-blind, placebo-controlled	EGb 761 (40 mg three times daily) or placebo	n=36 n=18 verum n=18 placebo 53-69 years	cerebro-organic Syndrome; Haschinsky-Score, EEG-theta ratio of 70% of the whole spectrum, saccadic latency more than 250 ms, maximum saccadic speed of 250°/s, saccade	quantitative EEG, saccadic test, Wiener Determination Test, ZVT	highly significant difference after 4 and also 8 weeks in saccadic test and psychometric tests (Wiener Determination Test and ZVT) on EGb 761 compared to placebo, saccade duration was shortened	after 4 weeks clearly positive attitude in verum group; 3 AE in EGb 761 and 2 in placebo group; no drop out

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
				duration more than 150 ms, Wiener Determination Test (less than 160 correct reactions in level 10, 168 in level 12, 175 in level 15) and ZVT (more than 28 seconds for completing the test)		and latency reduced, number of correct answers in Wiener Determination Test and ZVT increased significantly on EGb 761, marked reduction in theta proportion of the theta/alpha ratio, all parameters tested largely unaffected under placebo	
Halama *et al.* 1988	12 weeks randomised, double-blind, placebo-controlled	EGb 761 (40 mg three times daily) or placebo	n=40 n=20 verum n=20 placebo 55-85 years	mild to medium cerebrovascular insufficiency; Hachinski score >7, Crichton scale level 1-3 (score 11-21)	SCAG score, descriptive: HIV (Hintergrundinterferenz-Verfahren), SKT, CCG (Craniocorpographie), symptom-rating	total SCAG score dropped on average by 9 points on EGb 761 and remained unchanged on placebo (difference between treatment groups p=0.00005), an effect in SCAG-items particularly on disturbances of short-	no drop out; 1 AE in verum group (mild to moderate headache)

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
						term memory and mental awareness, specific verum effect on the SKT, no effect shown on HIV and CCG, superior effects were also shown in the symptoms of dizziness, headaches and tinnitus	
Eckmann 1990	6 weeks randomised, double-blind, placebo-controlled	*Ginkgo biloba* extract (solution "Kaveri", three times daily, daily dosage 160 mg or rather 40 mg ginkgoflavon glycosides) or placebo	n=58 n=29 verum n=29 placebo 41-71 years	cerebral insufficiency and the leading symptom depressive mood	changes in 12 typical symptoms after 2, 4 and 6 weeks	small but progressive improvements on placebo, overall number of improvements significantly larger on *Ginkgo biloba*, after 2 weeks differences in only a few of the symptoms, after 4 and 6 weeks differences in 11 of the 12 symptoms, largest number of improvements on ginkgo between week 2 and 4 ($^2/_3$ of patients)	not indicated

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
Mazza *et al.* 2006	24 weeks randomised, double-blind, placebo-and donepezil controlled	*Ginkgo biloba* special extract E.S. (Flavogin, 160 mg daily-no further details) or donepezil (5 mg daily-no further details) or placebo	n=76 n=25 ginkgo n=25 donepezil n=26 placebo 50-80 years	mild to moderate dementia; mean score of 3-5 on the Brief Cognitive Rating Scale, Hachinski Ischemic Score of <4, IQ>80 (global assessment), SKT score between 8 and 23, MMSE score between 13 and 25 (inclusive)	SKT, CGI, CGI-2, MMSE	no significant change for MMSE scores, EGb 761 and donepezil group show significant difference of SKT and CGI scores after treatment compared with placebo (p=0.01)	5 drop outs on *Ginkgo biloba* not imputable to AE and 4 drop outs on donepezil due to AE
Schneider *et al.* 2005	26 weeks randomised, double-blind, placebo-controlled, parallel	EGb 761 (60 mg or 120 mg twice daily) or placebo	n=513 n=169 verum (120 mg) n=170 verum (240 mg) n=174 placebo ≥60	mild to moderate dementia of the Alzheimer type	ADAS-cog, ADCS-CGIC	no differences between the treatment groups in cognitive endpoint, ADCS-CGIC did not differ significantly among treatment groups	Dizziness cases: EGb 761 120 mg group 17 (10.1%), EGb 761 240 mg group 11 (6.5%) and placebo group 12 (6.9%); in 4 out of 42 serious AE a causal relationship was considered “unlikely related” to the study

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
			years				drug; no dose effect was detected; no systematic changes or prolongation in bleeding time and blood coagulation; no interaction between EGb 761 and aspirin or warfarin in relevant subjects
Van Dongen *et al.* 2000	24 weeks randomised, double-blind, placebo-controlled, parallel, after 12 weeks ginkgo users were randomised once again to continued ginkgo or	EGb 761 (80 or 120 mg twice daily) or placebo	n=214 n=84 verum (160 mg) n=82 verum (240 mg) n=48 placebo ≥50 years	dementia (either AD or VaD; mild to moderate degree) or age-associated memory impairment	NAI-ZVT-G, NAI-ZN-G, NAI-WL, SCAG, GDS, self-perceived health and memory status, and behavioural assessment	no effect on each of the outcome measures for patients on ginkgo compared to placebo	first part: AE were 56%, 52%, and 44% for the ginkgo 240 mg, ginkgo 160 mg, and placebo groups, respectively; most common: dizziness (n=58), nervousness (n=49), headache (n=32); second part: rates of AE were 46%, 40% and 65%; 35 serious AE during entire trial period (one possible association

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
	placebo treatment						with study treatment, placebo user)
McCarney *et al.* 2008	6 months randomised, double-blind, placebo-controlled, parallel	EGb 761 (60 mg twice daily) or placebo	n=176 n=88 verum n=88 placebo ≥55 years	mild to moderate dementia; ≥55 years, presence of a carer, informed consent, sufficient command of English, clinical diagnosis of dementia, MMSE score of 12-26 inclusive, living in Greater London and adjoining regions	cognitive functioning (ADAS-Cog), participant and carer-rated quality of life (QOL-AD)	no significant effect between treatment groups on any primary endpoint	total of 63 AE, 29 (placebo group) and 28 (ginkgo group); one fatal cerebral haemorrhage in ginkgo group
Grass-Kapanke *et al.* 2011	12 weeks randomised, double-blind, placebo-controlled, parallel	EGb 761 (240 mg once daily) or placebo	n=300 n=150 verum n=150 control 45-65 years	very mild cognitive impairment (vMCI), subjective complaints of impairment, low functioning in at least one of the cognitive tests, perceived impairment for at least 3 months, total score above 23 in the	efficacy and tolerability of EGb 761 in subjects, (measure of attention and of memory, perceived physical health)	EGb 761 improved cognitive functioning and aspects of quality of life	most frequently gastrointestinal symptoms and infections and infestations; no serious AE

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
				MMSE, intact activities of daily living, no indication of dementia			
DeKosky *et al.* 2008	6.1 years randomised, double-blind, placebo-controlled, parallel	EGb 761 (120 mg twice daily) or placebo	n=3069 n=1545 verum n=1524 placebo ≥75 years	normal cognition or MCI, ≥75 years	diagnosis of dementia by DSM-IV criteria	16.1% in placebo group were diagnosed with dementia and 17.9% in EGb 761 group	no statistically significant differences in rate of serious AE; mortality rate was similar in the two treatment groups
Bäurle *et al.* 2009	6 weeks open	*Ginkgo biloba* fresh plant extract (90 mg twice daily)	n=59 >60 years	MCI, > 60 years, DemTect score >12, no obvious symptoms of dementia in the judgement of the investigator, signed informed consent, at least two of the following symptoms: forgetfulness, impaired concentration, or impaired memory,	DemTect (mental performance), SF-12 (quality of life), 5-point scale (change in symptoms), 4-point scale (assessing efficacy by the patient and the investigator), questioning of retreatment (acceptance of treatment)	no significant change in DemTect and SF-12 physical subscore, SF-12 mental subscore increased significantly by 3 points to 51.5±7.9 (p=0.013), symptoms improved in 41.3% (forgetfulness), 43.1% (impaired concentration), and 34.5% (impaired memory), 61% of the	39 AE; only one gastrointestinal disturbances and 18 AE were evaluated as possibly related to the medication, transient and mild to moderate in nature; treatment was tolerated well to very well in 83%; 6.8% were dissatisfied with the tolerability

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
				medication for improvement of mental performance was only allowed if it had been taken at a regular dosage for more than 4 weeks prior to start of the study		patients assessed efficacy as good or rather good, 28.8% noticed no effect, investigators rated tablets as effective or very effective in 69.4%, and as not effective in 23.7%, 90% would take the tablets again	
Vellas *et al.* 2012	5 years randomised, double-blind, placebo-controlled, parallel	EGb 761 (120 mg twice daily) or placebo	n=2854 n=1406 verum n=1414 placebo ≥70 years	spontaneously reported memory complaints to primary-care physician	conversion to probable AD	61 participants (1.2 cases per 100 person-years) in the *Ginkgo biloba* group and 73 (1.4 cases per 100 person-years) in the placebo group had been diagnosed with probable AD (hazard ratio 0.84, 95% CI 0.6-1.18; p=0.306)	Death, stroke and incidence of other haemorrhagic or vascular events did not differ between groups

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
Brautigam *et al.* 1998	24 weeks randomised, double-blind, placebo-controlled	Geriaforce, fresh plant extract (ethanol 70% V/V, DER 1:4, total flavone glycosides 0.2 mg/ml, total ginkgolides 0.34 mg/ml), high dose (HD): 40 drops ginkgo extract three times daily, low dose (LD): 40 drops ginkgo extract 1:1 with placebo three times daily or placebo	n=241 n=77 high dose n=82 low dose n=82 placebo 55-86 years	Memory and/or concentration complaints	EMCT, Benton Test, Rey Test part 1, BDI, Rey Test part 2, subjective perception of memory and concentration	in subjective test, EMCT, Rey 1 and Rey 2 no significant differences in improvement between groups, in Benton test increases of 18%, 26% and 11% in the HD, LD and placebo group, respectively	most frequently side effects were gastrointestinal complaints; no differences in the number of these side effects between placebo and verum group; dizziness: HD group 3, LD group 4 and placebo 0 cases; among drop outs 3 cases in the HD group, 1 in LD group and 3 on placebo

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
Kaschel 2011	6 weeks randomised, double-blind, placebo-controlled, parallel	EGb 761 (240 mg once daily) or placebo	n=188 n=94 verum n=94 placebo 45-65 years	mentally healthy, aged 45-65, higher-level secondary education (at least middle or high school), sufficient language skills to understand and respond to interview questions and undergo neuropsychological testing without difficulties and without assistance, who had provided written informed consent	assess effects on long-term memory, replicate evidence suggesting that objective improvement is paralleled by changes in subjective memory ratings, link changes in objective psychometric test performance with everyday life in terms of ecological validity	significant improvement in quantity and quality of recall of appointments, no superiority of ginkgo in another everyday memory test (recognition of a driving route)	low incidence of AE and not significantly different between treatment groups
Dodge *et al.* 2008	42 months randomised, double-blind, placebo-controlled	*Ginkgo biloba* extract (GBE, at least 6% terpene lactones and	n=118 n=60 verum n=58 placebo ≥85 years	normal elderly, ≥85 years, informant available, no subjective memory complaint, normal memory function, MMSE score >23,	mild cognitive decline (defined as CDR from 0 to 0.5), decline in memory function (Word List Delayed Recall test), adverse events	14 cases among placebo and 7 cases among GBE group progressed to CDR=0.5, GBE group showed a tendency of less decline in memory	GBE group had more stroke or TIA incidences (p=0.01), all strokes were non-haemorrhagic infarcts except one case, no deaths due to stroke; dizziness: GBE

Study	Treatment duration Study design	Study and control drugs, daily dose	Number of subjects by arms, age	Diagnosis, inclusion criteria	Primary endpoints	Efficacy results	Safety results
		24% flavone glycosides) 80 mg three times daily or placebo		CDR=0, CES-D-10 >4		function, no difference in adverse events (p=0.44)	group 2 (3.3%) and placebo group 2 (5.2%)

The following table summarises relevant data from the table above concerning the age associated meaning of dementia. Most studies are conducted with patients aged 50 and older. Four studies included patients with a minimum age of 41 (one study) or rather 45 (three studies). No data are given about the number of patients with corresponding age. To compare the mean age the lowest mean age of the older age studies is 63 years. In comparison to the studies with patients aged 41 or rather 45 the mean age is in the range of 54-56, except one study by Le Bars et al (1997). In this trial the mean age (69 years) is in the range of the mean age of studies with older aged patients. The three studies, which show no comparable mean age to the rest of the studies, include a low number of patients or a diagnosis which has no relevance in supporting the monograpf relevant indication.

Study	Patients (No.)	Age	Diagnosis	Efficacy results
Herrschaft *et al.* 2012	n=410	≥50 years Mean age: 65 years	Mild to moderate AD or VaD associated with neuropsychiatric symptoms	Improvement of 2.2±3.5 points on the SKT in the EGb 761 group and 0.3±3.7 points on placebo, NPI score improved by 4.6±7.1 in the EGb 761 group and by 2.1±6.5 in the placebo group, both drug-placebo comparisons were significant at p<0.001
Ihl *et al.* 2010a	n=404	≥50 years Mean age: 65 years	Mild to moderate dementia with neuropsychiatric features	Improvement of SKT score in 32% in the EGb 761 group and in 15% in the placebo group, improvement of NPI total score in 45%in the

Study	Patients (No.)	Age	Diagnosis	Efficacy results
				EGb 761 group and 24% in placebo group, significant superiority of EGb 761 over placebo in both primary endpoints (p<0.001)
Napryeyenko and Borzenko 2007	n=391	≥50 years Mean age: placebo group 63 years, verum group 65 years	Mild to moderate dementia with neuropsychiatric features	Mean -3.2-point improvement in the SKT on EGb 761 and average deterioration by +1.3 points on placebo (p<0.001); EGb 761 was significantly superior to placebo with respect to all (primary and secondary)efficacy variables (p<0.001)
Yancheva *et al.* 2009	n=96	≥50 years Mean age: verum group 70 years, donepezil group 67 years and combined treatment group 69 years	AD and neuropsychiatric features	Improvement in all tests and rating scales in all groups, no statistically significant differences, relatively consistent but not significant, slight superiority of the combined treatment over the single drugs
Kanowski *et al.* 1996	n=156	≥55 years Mean age: placebo (male) 66, (female) 72 years, verum (male and female) 70 years	Mild to moderate primary degenerative dementia of the AH type or multi-infarct dementia (MID)	Responder rates in CGI and SKT higher under EGb 761 compared to placebo (p<0.05), in NAB tendency in favour of EGb 761 (p<0.1), frequency of therapy responders differed significantly in favour of EGb 761 (p<0.005) in Fisher's Exact Test
Heinen-Kammerer *et al.* 2005	n=683	65-80 years Mean age: standard group 74 years, verum group 75 years	Mild to moderate dementia	According to PLC a significant improvement in quality-of-life of care taking relatives (p<0.001) and patients (positive mood p=0.018, negative mood p<0.001) was observed in the ginkgo group
Le Bars *et al.* 1997	n=309	≥45 years Mean age: both groups 69 years	Mildly to severely demented patients with AD or multi-infarct dementia	50% of EGb 761 group completed the study and 38% of placebo group; no significant change in the ADAS-Cog for EGb 761 group, a significant worsening of 1.5 points (p=0.006) on placebo; mild improvement in the GERRI on EGb 761, significant

Study	Patients (No.)	Age	Diagnosis	Efficacy results
				worsening on placebo (0.08 points; p=0.02), statistically significant difference in favour of EGb 761 (p=0.004); slight worsening for both treatment groups on the CGIC; AD subgroup analysis: similar results for both treatments, differences were significant on ADAS-Cog (p=0.02) and GERRI (p<0.001)
Hofferberth 1989	n=36	53-69 years Mean age: both groups 63 years	Cerebro-organic Syndrome	Highly significant difference after 4 and also 8 weeks in saccadic test and psychometric tests (Wiener Determination Test and ZVT) on EGb 761 compared to placebo, saccade duration was shortened and latency reduced, number of correct answers in Wiener Determination Test and ZVT increased significantly on EGb 761, marked reduction in theta proportion of the theta/alpha ratio, all parameters tested largely unaffected under placebo
Halama *et al.* 1988	n=40	55-85 years Mean age: placebo group 67 years, verum group 65 years	Mild to medium cerebrovascular insufficiency	Total SCAG score dropped on average by 9 points on EGb 761 and remained unchanged on placebo (difference between treatment groups p=0.00005), an effect in SCAG-items particularly on disturbances of short-term memory and mental awareness, specific verum effect on the SKT, no effect shown on HIV and CCG, superior effects were also shown in the symptoms of dizziness, headaches and tinnitus
Eckmann 1990	n=58	41-71 years Mean age: placebo group 54 years, verum group 56 years	Cerebral insufficiency and the leading symptom depressive mood	Small but progressive improvements on placebo, overall number of improvements significantly larger on *Ginkgo biloba*, after 2 weeks differences in only a few of the symptoms, after 4 and 6 weeks

Study	Patients (No.)	Age	Diagnosis	Efficacy results
				differences in 11 of the 12 symptoms, largest number of improvements on ginkgo between week 2 and 4 ($^2/_3$ of patients)
Mazza *et al.* 2006	n=76	50-80 years Mean age: placebo group 70 years, verum group 66 years, donepezil group 65 years	Mild to moderate dementia	No significant change for MMSE scores, EGb 761 and donepezil group show significant difference of SKT and CGI scores after treatment compared with placebo (p=0.01)
Schneider *et al.* 2005	n=513	≥60 years Mean age: placebo and verum group II 78 years, verum group I 79 years	Mild to moderate dementia of the Alzheimer type	No differences between the treatment groups in cognitive endpoint, ADCS-CGIC did not differ significantly among treatment groups
Van Dongen *et al.* 2000	n=214	≥50 years Mean age: all groups 83 years	Dementia (either AD or VaD; mild to moderate degree) or age-associated memory impairment	No effect on each of the outcome measures for patients on ginkgo compared to placebo
McCarney *et al.* 2008	n=176	≥55 years Mean age: placebo group 80 years, verum group 79 years	Mild to moderate dementia	No significant effect between treatment groups on any primary endpoint
Grass-Kapanke *et al.* 2011	n=300	45-65 years Mean age: 55 years	Very mild cognitive impairment (vMCI)	EGb 761 improved cognitive functioning and aspects of quality of life
DeKosky *et al.* 2008	n=3069	≥75 years Mean age: 79 years	Normal cognition or MCI	16.1% in placebo group were diagnosed with dementia and 17.9% in EGb 761 group
Bäurle *et al.* 2009	n=59	>60 years Mean age: 72 years	MCI	No significant change in DemTect and SF-12 physical subscore, SF-12 mental subscore increased

Study	Patients (No.)	Age	Diagnosis	Efficacy results
				significantly by 3 points to 51.5±7.9 (p=0.013), symptoms improved in 41.3% (forgetfulness), 43.1% (impaired concentration), and 34.5% (impaired memory), 61% of the patients assessed efficacy as good or rather good, 28.8% noticed no effect, investigators rated tablets as effective or very effective in 69.4%, and as not effective in 23.7%, 90% would take the tablets again
Vellas *et al.* 2012	n=2854	≥70 years Mean age: both groups 76 years	Spontaneously reported memory complaints to primary-care physician	61 participants (1.2 cases per 100 person-years) in the *Ginkgo biloba* group and 73 (1.4 cases per 100 person-years) in the placebo group had been diagnosed with probable AD (hazard ratio 0.84, 95% CI 0.6-1.18; p=0.306)
Brautigam *et al.* 1998	n=241	55-86 years Mean age: all three groups 69 years	Memory and/or concentration complaints	In subjective test, EMCT, Rey 1 and Rey 2 no significant differences in improvement between groups, in Benton test increases of 18%, 26% and 11% in the HD, LD and placebo group, respectively
Kaschel 2011	n=188	45-65 years Mean age: placebo group 55 years, verum group 54 ears	Mentally healthy	Significant improvement in quantity and quality of recall of appointments, no superiority of ginkgo in another everyday memory test (recognition of a driving route)
Dodge *et al.* 2008	n=118	≥85 years Mean age is not given	Normal elderly	14 cases among placebo and 7 cases among GBE group progressed to CDR=0.5, GBE group showed a tendency of less decline in memory function, no difference in adverse events (p=0.44)

4.2.2.1. Cognitive decline / Dementia syndrome

The author's conclusion of the English version of the executive summary of the IQWiG final report A05-19B: For the therapy goal "activities of daily living", there is evidence of a benefit of high-dose (240 mg daily) ginkgo extract EGb 761. In patients taking this dose, there are also indications of a benefit for the therapy goals "cognitive function" and "general psychopathological symptoms", as well as for the caregiver-relevant therapy goal "quality of life of caregivers" (measured on the basis of caregivers' emotional stress). However, the conclusion that ginkgo has a beneficial effect is based on very heterogeneous results; therefore no summarising conclusion can be made on the potential effect size. In addition, there is an indication that this benefit is only present in patients with accompanying psychopathological symptoms. Moreover, it needs to be considered that the results were strongly affected by 2 studies conducted in Eastern European health-care setting with specific patient populations (among other things, patients with a high rate of accompanying psychopathological symptoms).

Due to the high heterogeneity between studies, no conclusive statement can be made on the benefit of low-dose ginkgo (120 mg daily). Relevant data on ginkgo extracts other than ginkgo extract EGb 761 were not available.

The benefit of ginkgo compared with other drugs approved for Alzheimer's disease (such as cholinesterase inhibitors or memantine) is unclear, as only one explorative study investigated a direct comparison (vs. donepezil).

Despite the consideration of the ginkgo dose in the interpretation of results, the considerable heterogeneity could not be adequately explained. An assessment of the effect size was not possible on the basis of the available study data. Additional studies designed specifically to investigate individual subgroups of patients with Alzheimer's disease are needed to enable subgroup-specific conclusions to be drawn. As the results of this benefit assessment were dominated by 2 studies that were not conducted in the health-care setting of a Western country, future studies should be carried out in such a setting. If, due to available treatment options (e.g., cholinesterase inhibitors), placebo-controlled studies seem difficult to conduct, appropriate comparator studies with other antidementiva drugs could be an alternative option. Data from long-term studies would also be desirable to assess potential beneficial and adverse effects of long-term therapy with ginkgo **(Institute for Quality and Economic Efficiency in the Healthcare System 2008)**.

Study	**Herrschaft *et al.* 2012**	
Indication	mild to moderate AD or VaD associated with neuropsychiatric symptoms	
Treatment duration	24 weeks	
Test product	EGb 761	
Single / Daily dosage	240 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	n=17
	number of patients	410 randomised; 205 (EGb 761), 205 (placebo)
	age	≥50 years
	wash-out	4 weeks

Outcome	Patients treated with EGb 761 improved by 2.2±3.5 points (mean ± sd) on the SKT total score, whereas those receiving placebo changed only slightly by 0.3±3.7 points. The NPI composite score improved by 4.6±7.1 in the EGb 761-treated group and by 2.1±6.5 in the placebo group. Both drug-placebo comparisons were significant at p<0.001. Patients in the EGb 761 group also showed a more favourable course in most of the secondary efficacy variables (ability to cope with the demands of everyday living, quality of life and clinicians' global judgement). Author's conclusion: Treatment with EGb 761 at a once daily dose of 240 mg was safe and resulted in a significant and clinically relevant improvement in cognition, psychopathology, functional measures and quality of life of patients and caregivers.

Study	**Ihl *et al.* 2010a**	
Indication	Mild to moderate dementia with neuropsychiatric features (probable Alzheimer's disease (AD) according to National Institute of Neurological and Communicative Disorders and Stroke/ AD and Related Disorders Association (NINCDS-ADRDA), possible AD with cerebrovascular disease (CVD) according to National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l`Enseignement en Neurosciences (NINDS-AIREN) or probable vascular dementia (VaD) according to (NINDS-AIREN)); scoring 35 or lower in the Test for Early Detection of Dementia with Discrimination from Depression (TE4D), between 9 and 23 on the Syndrom Kurz Test (SKT), at least 5 on the Neuropsychiatric Inventory (NPI), with at least on item score of 3 or more, but below 20 on the Hamilton Rating Scale for Depression (HAMD)	
Treatment duration	24 weeks	
Test product	EGb 761	
Single / Daily dosage	240 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=20
	number of patients	202 (EGb 761); 202 (placebo)
	age	≥50 years
	wash-out	up to 4 weeks
Outcome	Patients treated with EGb 761 improved by -1.4 (95% CI -1.8; -1.0) points on the SKT and by -3.2 (-4.0; -2.3) on the NPI total score, whereas those receiving placebo deteriorated by +0.3 (-0.1; 0.7) on the SKT and did not change on the NPI total score (-0.9; 0.9). Both drug-placebo comparisons were significant at p<0.001. EGb 761 was significantly superior to placebo with respect to Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC), Activities of Daily Living International Scale (ADL-IS), NPI distress score, DEMQOL-Proxy quality-of-life scale and Verbal Fluency Test. Averse event rates were similar for both treatment groups.	

	Author's conclusion: EGb 761, 240 mg once daily, was found significantly superior to placebo in the treatment of patients with dementia with neuropsychiatric symptoms.

Study	**Ihl *et al.* 2010b**
	Retrospective analysis of data from the above mentioned trial
Outcome	Correlations between changes from baseline and NPI baseline scores were weak to modest, but conspicuously different between active drug and placebo groups. The slopes of the regression lines for the EGb 761 and the placebo groups showed qualitative and statistically significant differences: With increasing NPI baseline scores there was faster deterioration in the placebo group and thus more net benefit from treatment for the EGb 761 group. EGb 761 was effective in the treatment of dementia irrespective of the severity of neuropsychiatric symptoms.

Study	**Ihl *et al.* 2011**
	Subgroup analyses of the above mentioned study
Outcome	EGb 761 treatment was superior to placebo with respect to the SKT total score (drug-placebo differences: 1.7 for AD, $p<0.001$, and 1.4 for VaD, $p<0.05$) and the NPI total score (drug-placebo differences: 3.1 for AD, $p<0.001$ and 3.2 for VaD, $p<0.05$). Significant drug-placebo differences were found for most secondary outcome variables (ADCS-CGIC, ADL-IS, the DEMQOL-proxy quality of life scale, and the Verbal Fluency Test) with no major differences between AD and VaD subgroups. Rates of adverse effects were essentially similar in both groups. Author's conclusion: EGb 761 improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia.

Study	**Bachinskaya *et al.* 2011**
	Secondary analyses of data from the above mentioned study
Outcome	Primary outcome: NPI composite score improved by -3.2 (95% CI -4.0 to -2.3) in patients taking EGb 761, no change (-0.9; 0.9) in those receiving placebo Secondary outcome: NPI distress score (evaluate caregiver's distress) revealed similar baseline pattern and improvements Author's conclusion: Treatment with EGb 761, at once-daily dose of 240 mg, was safe, effectively alleviated behavioural and neuropsychiatric symptoms in patients with mild to moderate dementia, and improved the wellbeing of their caregivers.

Study	Napryeyenko and Borzenko 2007	
Indication	Mild to moderate dementia with neuropsychiatric features (probable AD (NINCDS-ADRDA), possible AD (NINCDS/ADRDA) with CVD (NINDS-AIREN) or probable VaD (NINDS-AIREN))	
Treatment duration	22 weeks	
Test product	EGb 761	
Single / Daily dosage	120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=16
	number of patients	400 randomised; study completed: 196 (EGb 761), 195 (placebo)
	age	≥50 years
	wash-out	up to 4 weeks
Outcome	There was a mean -3.2-point improvement in the SKT upon EGb 761 treatment and an average deterioration by +1.3 points on placebo ($p<0.001$, two sided, ANOVA). EGb 761 was significantly superior to placebo on all secondary outcome measures, including the NPI and an activities-of-daily-living scale. Treatment results were essentially similar for AD and VaD subgroups. The drug was well tolerated; adverse events were no more frequent under drug than under placebo treatment. Author's conclusion: The data add further evidence on the safety and efficacy of EGb 761 in the treatment of cognitive and non-cognitive symptoms of dementia.	

Study	Napryeyenko *et al.* 2009
	Secondary analyses of the above mentioned trial
Outcome	Under EGb 761 treatment the SKT total score improved by -3.0±2.3 and -3.4±2.3 points in patients with AD and VaD, respectively, whereas the patients on placebo deteriorated by +1.2±2.5 and 1.5±2.2 points, respectively ($p<0.01$ for both drug-placebo differences). Significant drug-placebo differences were found for all secondary outcome variables with no major differences between AD and VaD subgroups. The rate of adverse events tended to be higher for the placebo group. Author's conclusion: The subgroup analyses demonstrated that EGb 761 was safe and effective in the treatment of both major types of dementia, AD and VaD.

Study	Scripnikov *et al.* 2007
	Detailed description of the effects of EGb 761 on the various neuropsychiatric symptoms of dementia of data from the above mentioned trial
Outcome	The mean composite score (frequency x severity) and the mean caregiver

	distress score of the NPI dropped from 21.3±9.5 to 14.7±9.5 and from 13.5±6.7 to 8.7±5.5, respectively, in the EGb 761-treated patients, but increased from 21.6±9.9 to 24.1±12.8 and 13.4±6.4 to 13.9±7.2, respectively, under placebo (p<0.001). The largest drug-placebo differences in favour of EGb 761 were found for apathy/indifference, anxiety, irritability/lability, depression/dysphoria and sleep/nighttime behaviour. Author's conclusion: EGb 761 was safe and effective in the treatment of dementia with neuropsychiatric symptoms.

Study	**Kanowski *et al.* 1996**	
Indication	Mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia (MID); SKT score: 6-18; MMSE score: 13-25	
Treatment duration	24 weeks	
Test product	EGb 761	
Single / Daily dosage	120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=41
	number of patients	216 (ITT: 205; per-protocol (PP):156)
	age	≥55 years
	wash-out	4 weeks
Outcome	The frequency of therapy responders in the two treatment groups differed significantly in favour of EGb 761, with p<0.005 in Fisher's Exact Test. The intent-to-treat analysis led to similar efficacy results. Author's conclusion: The clinical efficacy of EGb 761 in dementia of the Alzheimer type and multi-infarct dementia was confirmed. The investigational drug was found to be well tolerated.	

Study	**Kanowski and Hoerr 2003**
	Detailed ITT analysis of all patients and for the subgroup of probable dementia of the Alzheimer type (DAT) patients of data from the above mentioned study
Outcome	ITT analysis of the total population: The ITT analysis of the SKT and estimated AD Assessment Scale-cognition (ADAS-cog) scores revealed a mean decrease in the total score by -2.1 (95% CI: -2.7; -1.5) points and -2.7 (95% CI: -3.5; -1.9) points, respectively, for the EGb 761 group, which indicates an improvement in cognitive function. On the contrary, the placebo group exhibited only a minimal change of -1.0 (95% CI: -1.6; -0.3) and -1.3 (95% CI: -2.0; -0.4) points, respectively. The changes from baseline differed significantly between treatment groups by 1.1 (SKT) and 1.4 (estimated ADAS-cog) points, respectively (p=0.01). The Clinical Global Impression of Change favoured the EGb 761 group with a mean

	difference of 0.4 points (p=0.007). Changes in the rating related to activities of daily living (Nürnberger-Alters-Beobachtungs-Skala, NAB) showed a favourable trend for EGb 761. ITT analysis of patients with DAT: Using a decrease of at least 4 points on the estimated ADAS-cog scores as cutoff criterion for treatment response, 35% of EGb 761-treated patients were considered responders versus only 19% for the placebo group (p=0.01) Author's conclusion: The results substantiate the outcomes previously obtained with a responder analysis of the PP population and confirm that EGb 761 improves cognitive function in a clinically relevant manner in patients suffering from dementia.

Study	**Heinen-Kammerer *et al.* 2005**	
Indication	Mild to moderate dementia; MMST: 12-24	
Treatment duration	12 months	
Test product	EGb 761	
Single / Daily dosage	no dose mentioned	
Study design	randomised	no
	double-blind	no (open)
	controlled	yes (standard)
	parallel group	yes
	multicentre	yes
	number of patients	281 (Ginkgo-cohort), 402 (Standard-cohort)
	age	65-80 years
	wash-out	-
Outcome	According to Profile of quality of life of chronically ill (PLC) a significant improvement in quality-of-life of care-taking relatives (p<0.001) and patients (positive mood p=0.018, negative mood p<0.001) was only observed in the ginkgo-cohort. Barthel-Index indicated an improvement in the ginkgo-cohort (p<0.001). MMST-scores increased in significantly only in the ginkgo-cohort (p<0.001). Author's conclusion: EGb 761 attributes to a higher quality of life for both care-takers and patients and the progression of disease is slowed down.	

Study	**Le Bars *et al.* 1997**	
Indication	Mildly to severely demented patients with AD or multi-infarct dementia, without other significant medical conditions	
Treatment duration	52 weeks	
Test product	EGb 761	
Single / Daily dosage	40 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=6

	number of patients	309 (ITT); 202 (end point analysis)
	age	≥45 years
	wash-out	2 weeks
Outcome	ITT analysis: The EGb 761 group had an ADAS-cog score 1.4 points better than the placebo group (p=0.04) and a Geriatric Depression Scale (GERRI) score 0.14 points better than the placebo group (p=0.004). End point analysis: The same patterns were observed with the evaluable data set in which 27% of patients treated with EGb 761 achieved at least a 4-point improvement on the ADAS-cog, compared with 14% taking placebo (p=0.005); on the GERRI, 37% were considered improved with EGb 761, compared with 23% taking placebo (p=0.003). No difference was seen in the Clinical Global Impression of Change (CGIC). No significant differences compared with placebo were observed in the number of patients reporting adverse events or in the incidence and severity of these events. Author's conclusion: EGb 761 was safe and appears capable of stabilising and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year. Although modest, the changes induced by EGb 761 were objectively measured by the ADAS-cog and were of sufficient magnitude to be recognised by the caregivers in the GERRI.	

Study	**Hofferberth 1989**	
Indication	Classical symptoms of organic syndrome such as dizziness, memory and concentration loss, and orientation disorders	
Treatment duration	8 weeks	
Test product	EGb 761	
Single / Daily dosage	40 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	36 (18 each group)
	age	53-69 years
	wash-out	2 weeks
Outcome	A highly significant difference could be seen in the results of the saccadic test and the psychometric tests compared to the placebo control group. Saccade duration was shortened and the latency reduced. In parallel, the number of correct answers given in the Wiener Determination Test and Number Connection Test increased significantly compared to the control group. A marked reduction in the theta proportion of the theta/alpha ratio was found. All the parameters tested remained largely unaffected under placebo therapy. Author's conclusion: EGb 761 is significantly more effective than placebo and confirms the favourable results obtained to date in this indication area.	

Study	**Halama *et al.* 1988**	
Indication	Mild to medium cerebrovascular insufficiency; Hachinski score: >7; Crichton: level 1 to 3	
Treatment duration	12 weeks	
Test product	EGb 761	
Single / Daily dosage	40 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	no
	number of patients	40
	age	55-85 years
	wash-out	-
Outcome	In the EGb 761 group, the values for total Sandoz Clinical Assessment-Geriatric (SCAG) score dropped on average by 9 points, whereas they remained unchanged in the placebo group ($p=0.00005$, one-sided, X^2-test). Evaluation of the separate items showed an effect particularly on disturbances of short-term memory and mental awareness as well as on dizziness as a symptom.	

Study	**Eckmann 1990**	
Indication	Cerebral insufficiency and the leading symptom depressive mood	
Treatment duration	6 weeks	
Test product	*Ginkgo biloba* extract (drops, not further specified)	
Single / Daily dosage	53.33 mg/160 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	no
	number of patients	58 (29 each group)
	age	41-71 years
	wash-out	-
Outcome	In the group receiving placebo, small, but progressive improvements were observed. In the *Ginkgo biloba* group, the overall number of improvements was significantly larger. After 2 weeks the differences were marked for only a few of the symptoms; after 4 and 6 weeks in contrast, in 11 of the 12 symptoms. The largest number of improvements (two-thirds) in the *Ginkgo biloba* group was observed between the second and fourth weeks of treatment.	

Study	**Mazza *et al.* 2006**
Indication	Mild to moderate dementia
Treatment duration	24 weeks
Test product	*Ginkgo biloba* special extract E.S. (Flavogin)
Single / Daily dosage	160 mg daily dose

Study design	randomised	yes
	double-blind	yes
	controlled	yes (donepezil; placebo)
	parallel group	-
	multicentre	-
	number of patients	76
	age	50-80 years
	wash-out	-
Outcome	An improvement of MMSE scores was observed in the ginkgo group: mean value was from 18.80±3.622 (SD) at baseline to 19.40±3.485 (SD) at 24 weeks period. As regard SKT we observed an improvement of scores in the ginkgo group: mean values passed from 16.45±3.05 (SD) at baseline to 13.15±2.9 (SD) at 24 weeks. A statistical significance was observed for *Ginkgo biloba* extract and donepezil group in a t-test comparison; both groups show also a significant difference when compared with placebo group in an ANOVA. There was a significant difference in Clinical Global Impression (CGI) scores changes for donepezil and *Ginkgo biloba* group from baseline to the end of 24 weeks of treatment. Mean values passed from 4.65±0.87 (SD) to 3.75±0.96 (SD) for *Ginkgo biloba* group. Author's conclusion: The study suggests that there is no evidence of relevant differences in the efficacy of *Ginkgo biloba* extract and donepezil in the treatment of mild to moderate AD, so the use of both substances can be justified. In addition, this study contributes to establish the efficacy and tolerability of the *Ginkgo biloba* special extract E.S. in the dementia of the Alzheimer type with special respect to moderately severe stages.	

Korczyn (2007) commented some important aspects on the above mentioned article. The first two parameters he was missing were that it was not stated who supported the study (industry?) and who made the statistical calculations. Secondly, the primary and secondary end-points of the study were not mentioned and the main conclusions (the MMSE) were negative, which was not reflected in the paper. Also, results a long the way of the study are not shown, at which this is surprisingly as in studies of cholinesterase inhibitors the strongest effect is seen at 6-12 weeks. In the placebo 4-week run-in period it was not stated how placebo responders were determined and how many were rejected. The time point for baseline values was not stated. Last but not least the commentator was missing an analysis from the completers of the study as there were about 20% dropouts.

Mazza *et al.* (2007) replied as follows: The study was not supported by any pharmaceutical industry. The aim of the study was to assess the efficacy of *Ginkgo biloba* in moderately severe stages of AD. The results suggested an efficacy of ginkgo comparable with donepezil. Therefore the main conclusions were not negative, considering that patients treated with ginkgo showed an improvement in attention, memory and cognitive performance. Results after 6 and 12 weeks showed a significant efficacy and tolerability of ginkgo compared with donepezil.

Corrao *et al.* (2007) commented methodological matters on the article by Mazza *et al.* (2006): There was a small population sample studied and no effort was made to calculate sample size. Trials with small population samples have scare sensitivity and can bring to negative results (no differences between groups). Besides, a drop-out at follow-up ≥20% comprises the overall quality of a trial. In this case there was a drop-out of about 21%. Because there exist a lot of different types of ANOVA, it

must be stated what kind of ANOVA was used. Differences in resulting scores of SKT and MMSE (obviously not normally distributed) should be evaluated by distribution-free (non-parametric) statistical methods, like in this case, the Kruskal-Wallis test (a non-parametric ANOVA). The study had three groups and in no case pair-wise comparisons can be made by a t-test (only used if the study groups are exclusively two), hence comparison between the study groups need a post hoc evaluation test like Dwass-Steel-Critchlow-Fligner or Conover-Inman procedures. For all these reasons, no statements could be made on the efficacy of the two treatments. Moreover, this study cannot evaluate tolerability of *Ginkgo biloba* due to the small sample size and the short-time follow-up. Having pointed out these aspects, this study has scientific value, but readers should be advised of all these considerable limitations.

Reply by Mazza *et al.* (2007): It was already outlined in the "Discussion and conclusions" section that larger samples of patients should be considered to confirm these results. In the author's opinion this drop-out rate clearly reflects peculiar clinical features of enrolled patients, as psychiatrists and neurologists working in the field of dementia know. As for considerations regarding the statistical analysis section, a preliminary analysis of the data was conducted using the Shapiro-Wilk normality test (W), which checks of normal distribution. In the present case W was not significant, so the scientists were not obliged to use non-parametric methods. The authors do not assume that the results of this test is clear evidence of normality or non-normality, but, in such perspective, we used t-test comparing each group in two different times (baseline and after 24 weeks).

Study	**Yancheva *et al.* 2009**	
Indication	AD and neuropsychiatric features (NINCDS/ADRDA, score below 36 on the TE4D, score below 6 on the CDT and between 9 and 23 on the SKT; at least 5 on the 12-item NPI)	
Treatment duration	22 weeks	
Test product	EGb 761, donepezil or both	
Single / Daily dosage	120 mg/240 mg (EGb 761); 5 mg/5 mg (donepezil, first 4 weeks); 5 mg/10 mg (donepezil, remaining 18 weeks), and combined treatment (recommended doses)	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (donepezil)
	parallel group	yes
	multicentre	n=4
	number of patients	96 randomised; completed study: 30 (EGb 761), 29 (donepezil), and 29 (combined treatment)
	age	≥50 years
	wash-out	8 weeks
Outcome	Changes from baseline to week 22 and response rates were similar for all three treatment groups with respect to all outcome measures (SKT, NPI, total score and ADL sub-score of the GBS, HAMD, CDT and Verbal Fluency Test). An apparent tendency in favour of combination treatment warrants further scrutiny. Compared to donepezil mono-therapy, the adverse event rate was lower under EGb 761 treatment and even under the combination treatment. Author's conclusion: Three hypotheses were developed that will have to be	

	proven in further studies. First, there is no significant difference in the efficiency between EGb 761 and donepezil, second, a combination therapy will be superior to a mono-therapy with one of both substances and third, there will be fewer side effects under a combination therapy than under mono-therapy with donepezil.

Study	**Schneider *et al.* 2005**	
Indication	Mild to moderate dementia of the Alzheimer type (probable AD (NINCDS/ADRDA); dementia symptoms for at least 6 months; modified Hachinski ischemic score less than 4; MMSE score of 10 to 24	
Treatment duration	26 weeks	
Test product	EGb 761	
Single / Daily dosage	60 mg/120 mg or 120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=44
	number of patients	513 randomised; study completed: 135 (placebo), 135 (120 mg EGb 761), 140 (240 mg EGb 761)
	age	56-98 years (randomised patients)
	wash-out	4 weeks
Outcome	There were no significant between-group differences for the whole sample. There was little cognitive and functional decline of the placebo-treated patients, however. For a subgroup of patients with neuropsychiatric symptoms there was a greater decline of placebo-treated patients and significantly better cognitive performance and global assessment scores for the patients on EGb 761. Author's conclusion: The trial did not show efficacy of EGb 761, however, the lack of decline of the placebo patients may have compromised the sensitivity of the trial to detect a treatment effect. Thus, the study remains inconclusive with respect to the efficacy of EGb 761.	

Study	**Van Dongen *et al.* 2000**	
Indication	Dementia (either AD or VaD; mild to moderate degree) or age-associated memory impairment (AAMI)	
Treatment duration	24 weeks	
Test product	EGb 761	
Single / Daily dosage	120 mg/240 mg or 80 mg/160 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	yes
	number of patients	214; 48 (placebo), 84 (160 mg EGb 761), 82 (240 mg EGb 761)

	age	≥50 years
	wash-out	3 weeks (run-in period)
Outcome	An ITT analysis showed no effect on each of the outcome measures for participants who were assigned to EGb 761 (n=79) compared with placebo (n=44) for the entire 24-week period. After 12 weeks of treatment, the combined high dose and usual dose EGb 761 groups (n=166) performed slightly better with regard to self-reported ADL but slightly worse with regard to self-perceived health status compared with the placebo group (n=48). No beneficial effects of a higher dose or prolonged duration of EGb 761 treatment were found. There was no subgroup detected that benefited from EGb 761. EGb 761 use was also not associated with the occurrence of (serious) adverse events. Author's conclusion: The results of the trial suggest that EGb 761 is not effective as a treatment for older people with mild to moderate dementia or AAMI.	

Study	**Van Dongen *et al.* 2003**
	Analysis of the primary outcome measures of the above mentioned study
Outcome	There were no statistically significant differences in mean change of scores between EGb 761 and placebo. The differences were for SKT: +0.4 (90% CI -0.9-1.7), for CGI-2: +0.1 (90% CI -0.3-0.4), and for NAI-NAA: -0.4 (90% CI -1.9-1.2). A positive difference is in favour of EGb 761. Neither the dementia subgroup (n=36) nor the AAMI subgroup (n=87) experienced a significant effect of EGb 761 treatment. There was no dose-effect relationship and no effect of prolonged EGb 761 treatment. Author's conclusion: The trial did not support the view that EGb 761 has a beneficial effect for patients with dementia or AAMI.

Study	**McCarney *et al.* 2008**	
Indication	Mild to moderate dementia	
Treatment duration	6 months	
Test product	EGb 761	
Single / Daily dosage	60 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	-
	number of patients	176
	age	≥55 years
	wash-out	-
Outcome	*Ginkgo biloba* did not have a significant effect after 6 months on either the ADAS-cog score (p=0.392), the participant-rated QOL-AD score (p=0.787) nor the carer-rated QOL-AD score (p=0.222).	

	Author's conclusion: There was no evidence found that a standard dose of EGb 761 benefits in mild-moderate dementia over 6 months.

Study	**Grass-Kapanke *et al.* 2011**	
Indication	Very mild cognitive impairment (vMCI)	
Treatment duration	12 weeks	
Test product	EGb 761	
Single / Daily dosage	240 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=5
	number of patients	300
	age	45-65 years
	wash-out	-
Outcome	ITT analysis: Significant improvement ($p<0.025$, one-sided) beyond practice effects for EGb 761 in a measure of attention (WTS-ALS), trends in favour of EGb 761 in measures of memory (WMC III Faces I), and perceived physical health (SF-36); cognitive effects were more pronounced and more consistent ($p<0.025$ in 4 of 5 tests) in subjects with lower memory function at baseline; specifically, practice effects in the more demanding tests were attenuated or absent in these subjects Author's conclusion: EGb 761 improved cognitive functioning and aspects of quality of life in subjects with vMCI.	

Study	**DeKosky *et al.* 2008**	
Indication	Normal cognition or mild cognitive impairment (MCI)	
Treatment duration	6.1 years (2002-2008)	
Test product	EGb 761	
Single / Daily dosage	120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	yes (n=5)
	number of patients	2587 (normal cognition); 482 (MCI)
	age	≥75 years
	wash-out	-
Outcome	523 individuals developed dementia (246 receiving placebo and 277 receiving EGb 761) with 92% of the dementia cases classified as possible or probable AD, or AD with evidence of vascular disease of the brain. The overall dementia rate was 3.3 per 100 person-years in participants assigned to EGb 761 and 2.9 per 100 person-years in the placebo group. The hazard ratio for EGb 761 compared with placebo for all-cause dementia was 1.12 (95% CI, 0.94-1.33; p=0.21) and for AD, 1.16 (95% CI, 0.97-	

	1.39; p=0.11). EGb 761 also had no effect on the rate of progression to dementia in participants with MCI (HR, 1.13; 95% CI, 0.85-1.50; p=0.39). Author's conclusion: EGb 761 at 120 mg 2 times daily was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

Study	**Bäurle *et al.* 2009**	
Indication	Mild cognitive impairment	
Treatment duration	6 weeks	
Test product	*Ginkgo biloba* fresh plant extract (DER 3-5:1; extractant 65% ethanol V/V; produced in Switzerland)	
Single / Daily dosage	90 mg/180 mg	
Study design	randomised	-
	double-blind	no (open)
	controlled	-
	parallel group	-
	multicentre	n=11
	number of patients	59
	age	>60 years
	wash-out	-
Outcome	After 6 weeks the SF-12 mental score had increased significantly from 48.3±10.1 to 51.3±7.9, whereas the sf-12 body score (44.5±9.2 to 45.3±8.1) and the DemTect score (15.9±2.0 to 16.0±2.3) had not changed significantly. About half of all patients experienced an improvement in their memory and their ability to concentrate, as well as a decrease in symptoms of forgetfulness. The majority of investigators and patients judged the treatment to be effective. Author's conclusion: This newly developed, holistic fresh leaf extract of *Ginkgo biloba* is a safe, effective, and, at least, adjuvant treatment option for patients with mild cognitive impairments.	

Study	**Vellas *et al.* 2012**	
Indication	Spontaneously reported memory complaints	
Treatment duration	5 years	
Test product	EGb 761	
Single / Daily dosage	120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	n=13
	number of patients	2854 randomised, 1406 (EGb 761), 1414 (placebo)
	age	≥70 years
	wash-out	-

Outcome	Over 5 years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (1.2 cases per 100 person-years) compared with 73 participants in the placebo group (1.4 cases per 100 person-years; hazard ratio [HR] 0.84, 95% CI 0.6-1.18; p=0.306), but the risk was not proportional over time. Incidence of adverse events was much the same between groups. Death and stroke rate also incidence of other haemorrhagic or cardiovascular events did not differ between groups. Author's conclusion: Long-term use of standardised *Ginkgo biloba* extract in this trial did not reduce the risk of progression to Alzheimer's disease compared with placebo.

Study	**Brautigam *et al.* 1998**	
Indication	Memory and/or concentration complaints	
Treatment duration	24 weeks	
Test product	*Ginkgo biloba* alcohol/water extract (Geriaforce)	
Single / Daily dosage	high dose (HD): 40 drops (1.9 ml) undiluted ginkgo extract/120 drops (5.7 ml); low dose (LD): 40 drops (1.9 ml) ginkgo extract 1:1 with placebo/120 drops (5.7 ml)	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	n=22
	number of patients	241; 197 completed
	age	55-86 years
	wash-out	4 weeks
Outcome	In the subjective test, the EMCT, the Rey 1 and Rey 2 no significant differences in improvement in time between the groups were observed. In the Benton test increases of 18%, 26% and 11% (expressed as percentage of baseline scores) were observed in the HD, LD and placebo, respectively (MANOVA; p=0.0076). No substantial correlation was observed between subjective perception of the severeness of memory complaints and the objective test results. There were no differences in the amount of side effects between groups. Author's conclusion: It was demonstrated that a *Ginkgo biloba* alcohol/water extract is effective in elderly individuals with cognitive impairment.	

Study	**Kaschel 2011**
Indication	To investigate the effects of EGb 761 on memory and the specificity of such effects on distinct memory functions
Treatment duration	6 weeks
Test product	EGb 761
Single / Daily dosage	240 mg/240 mg

Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	no
	number of patients	188 randomised; full analysis set: 177, PP set: 159
	age	45-56 years
	wash-out	at least 8 weeks
Outcome	EGb 761-treated subjects improved significantly in quantity of recall (list of appointments; drug-placebo differences: p=0.038 for immediate and p=0.008 for delayed recall). Effects on qualitative recall performance were similar (drug-placebo differences: p=0.092 for immediate and p=0.01 for delayed recall). No superiority of ginkgo was evident in another everyday memory test which asked for recognition of a driving route (drug-placebo differences: p>0.1). The incidence of adverse events was low and not significantly different between treatment groups. Author's conclusion: EGb 761 (240 mg once daily) improves free recall of appointments in middle-aged healthy volunteers, which requires high demands on self-initiated retrieval of learned material. This function is known to be sensitive to normal aging, i.e., reduced in healthy middle-aged subjects. No effects are seen in a less demanding everyday memory task which does not tap this critical function.	

Study	**Dodge *et al.* 2008**	
Indication	No subjective memory complaint; normal memory function (Wechsler Memory Scale revised, WMS-R); Mini Mental State Examination (MMSE) score>23.6; Clinical Dementia Rating (CDR)=0; Center for Epidemiological Studies Depression Scale (CES-D-10)<4	
Treatment duration	42 months	
Test product	*Ginkgo biloba* extract (Thorne Research, Inc., Sandpoint, ID)	
Single / Daily dosage	80 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	118
	age	≥85 years
	wash-out	-
Outcome	Intention-to-treat analysis: No reduced risk of progression from CDR=0 to CDR=0.5 (log-rank test, p=0.06) among the *Ginkgo biloba* group; there was no less of a decline in memory function among the ginkgo group (p=0.05) Control of the medication adherence level: *Ginkgo biloba* group had a lower risk of progression from CDR=0 to CDR=0.5 (Hazard ratio (HR)=0.33, p=0.02), and a smaller decline in memory scores (p=0.04)	

	Author's conclusion: In unadjusted analyses, *Ginkgo biloba* extract neither altered the risk of progression from normal to CDR=0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a progression effect of *Ginkgo biloba* on the progression to CDR=0.5 and memory decline. Results of larger prevention trials taking into account medication adherence may clarify the effectiveness of *Ginkgo biloba* extract.

Reviews and meta-analyses:

Gertz and Kiefer (2004) concluded in the review of the, at that time, current and past literature that *Ginkgo biloba* extract has reproducible effects on cognitive functions in AD. There was no convincing evidence of beneficial effects in VaD, however methodologically sound studies are lacking in this field. The extremely low rate of side effects together with the knowledge of interesting mechanisms of action make *Ginkgo biloba* extract a promising substance for further clinical studies in AD and other dementing disorders.

Kaschel (2009) concluded that this review suggested evidence for a specific pattern of improvements achieved in randomised controlled group-studies using *Ginkgo biloba* extract. In spite of possible biases which cannot be ruled out in some trials, predominantly complex measures of memory, attention and intelligence improved. Significant changes occurred more often than expected by chance even after adjustment for number of comparisons and after correction for possible correlations between scores. Thus, the most influential factors which tend to produce α-errors could be controlled in this manner in this review. In contrary, β-errors are less discussed in other reviews though we can show that they occur frequently in the trials included and these β-errors seem to be the main source of the rather heterogeneous results. Therefore, ginkgo might not have had a fair chance to demonstrate specific effects in its chronic administration to non-demented subjects, as selection of psychometric tests was rarely theoretically or empirically grounded, samples were small, treatment duration was short and reliable and modern psychometric tests sensitive to deficits and sensitive to monitor change are often lacking. Replications are missing and researchers tend to use their own measures thus lowering the comparability and the number of replications available to date. If replications are reported, these yield rather consistent results (Mix and Crews, 2000, 2002). The specific pattern identified encourages future research and respective trials should not only concentrate on JADAD scores as the only index for methodological quality but take into account psychometric standards.

Birks (2009): Author's conclusion in the abstract of the Cochrane Review on "*Ginkgo biloba* for cognitive impairment and dementia (Review)" is as follows: *Ginkgo biloba* appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, or were small, and publication bias cannot be excluded. The evidence that *Ginkgo biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

Wang *et al.* (2010): Meta-analysis of clinical studies of the effectiveness of standardised *Ginkgo biloba* extract on cognitive symptoms of dementia

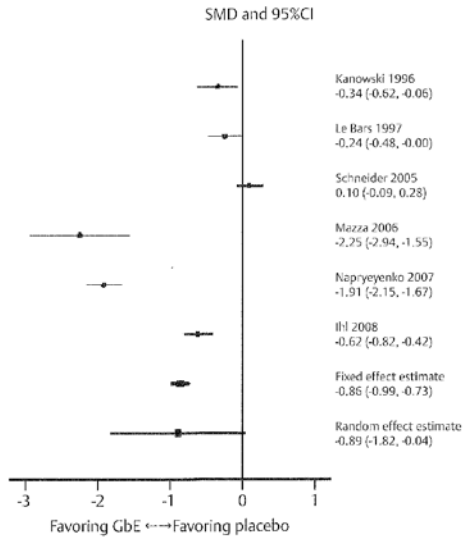


Fig. 1 Standard man difference (95% CI) of GbE vs placebo for effects on measures of cognition after 22–26 weeks of treatment.

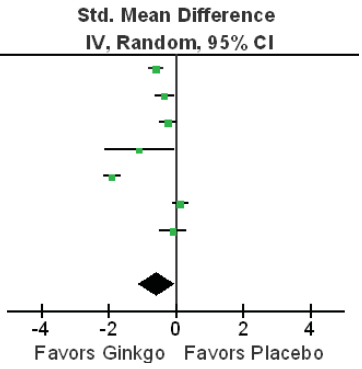
Author's conclusion: The bivariate random effect meta-analysis of 6 clinical studies demonstrated that standardised *Ginkgo biloba* extract could significantly improve the cognitive function of dementia disorders with the treatment period of 6 months when baseline risk was considered in assessing the efficacy of standardised *Ginkgo biloba* extract.

Weinmann *et al.* (2010): Meta-analysis of clinical studies of the effects of *Ginkgo biloba* in dementia

ITT/LOCF change scores for cognition outcomes (ADAS-cog, SKT):

	Ginkgo			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ihl 2008	-1.4	2.8	202	0.3	2.8	202	15.2%	-0.61 [-0.81, -0.41]
Kanowski 1996	-2.1	3.15	106	-1	3.05	99	14.9%	-0.35 [-0.63, -0.08]
LeBars 1997	-0.3	5.35	134	1	5.32	134	15.0%	-0.24 [-0.48, -0.00]
Maurer 1997	-2.9	2.5	9	0.8	3.8	9	10.3%	-1.10 [-2.10, -0.09]
Napryeyenko 2007	-3.2	2.3	198	1.3	2.4	197	15.0%	-1.91 [-2.15, -1.67]
Schneider 2005	1.6	5.8	169	0.9	5.6	174	15.1%	0.12 [-0.09, 0.33]
vanDongen 2000	0.8	4.1	79	1.2	3.8	40	14.4%	-0.10 [-0.48, 0.28]
Total (95% CI)			**897**			**855**	**100.0%**	**-0.58 [-1.14, -0.01]**

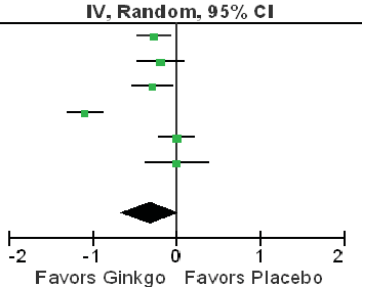
Heterogeneity: Tau² = 0.53; Chi² = 178.92, df = 6 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.01 (P = 0.04)



ITT/LOCF change scores for ADL outcomes:

	Ginkgo			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ihl 2008	-0.2	0.73	202	0	0.73	202	17.3%	-0.27 [-0.47, -0.08]
Kanowski 1996	-0.8	2.1	106	-0.4	2.03	99	16.5%	-0.19 [-0.47, 0.08]
LeBars 1997	-0.05	0.42	138	0.07	0.41	132	16.9%	-0.29 [-0.53, -0.05]
Napryeyenko 2007	-1.9	2.7	198	0.9	2.4	197	17.2%	-1.09 [-1.31, -0.88]
Schneider 2005	-0.1	0.4	169	-0.1	0.3	174	17.2%	0.00 [-0.21, 0.21]
vanDongen 2000	1.4	4.8	79	1.4	5.5	40	15.0%	0.00 [-0.38, 0.38]
Total (95% CI)			**892**			**844**	**100.0%**	**-0.32 [-0.66, 0.03]**

Heterogeneity: Tau² = 0.17; Chi² = 63.27, df = 5 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.77 (P = 0.08)

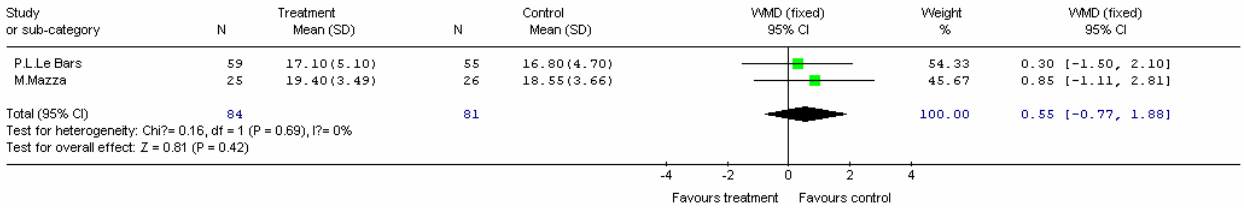


Author's conclusion: A statistically significant advantage of *Ginkgo biloba* compared to placebo in improving cognition for the whole group of patients with AD, vascular or mixed dementia was found. Regarding ADL, there was no significant difference for the whole group. However, in the subgroup of

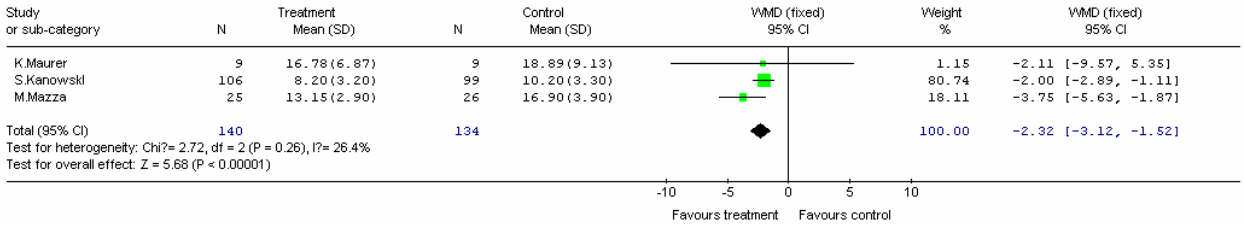
patients with AD, there was a statistically significant advantage of *Ginkgo biloba* compared to placebo. In a situation, where the clinical significance of the moderate effects of cholinesterase inhibitors and memantine as symptomatic treatments is increasingly been questioned, *Ginkgo biloba* may not be an inferior treatment option for a considerable number of people with mild to moderate dementia. However, direct comparisons are lacking. A major multicenter study to compare the relative effectiveness of *Ginkgo biloba* and cholinesterase inhibitors for different dementia subgroups appears justified.

Yang *et al.* (2011): Meta-analysis of *Ginkgo biloba* extract for the treatment of AD

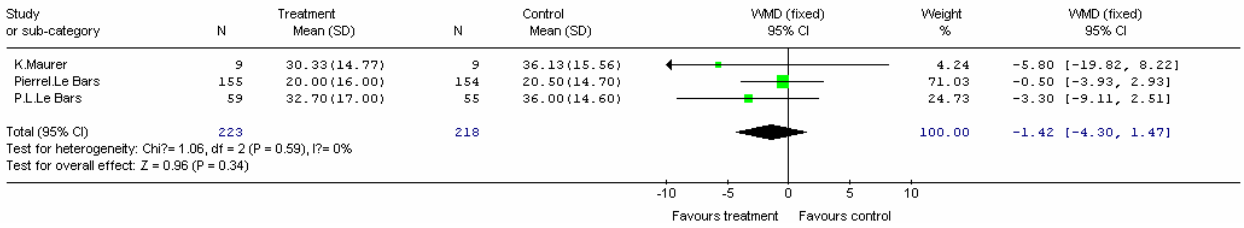
Meta-analysis of MMSE scores:



Meta-analysis of SKT scores:



Meta-analysis of ADAS-cog score:



Author's conclusion: *Ginkgo biloba* extract shows good therapeutic effects for mild and moderate AD.

Solomon and Michalczuk (2009) discussed the conflicting results of *Ginkgo biloba* studies emerged from the fact that there is no agreed upon set of standards by which to judge the efficacy of complementary and alternative medicines (CAM). On the basis of having no generally accepted guidelines to standardise the types of studies that are conducted in the field of cognition enhancement in both healthy elderly and patients with AD and other dementing disorders, the authors suggested a roadmap for establishing guidelines for the evaluation of CAM in cognition. They applied these guidelines to the conflicting literature on *Ginkgo biloba* to determine whether they might help resolve the conflicting results. The criteria suggested in the guidelines of this article are the generally accepted standards by both United States [draft guideline for the evaluation of antidementia compounds (Leber 1990) of the Division of Pharmacologic Drug Actions of the U.S. FDA] and European regulatory agencies [guidelines for evaluating the efficacy (and safety) of treatments for AD and other dementias] for clinical research. Applying the proposed guidelines to some of the literature that have led to the

controversy results invites the conclusion that *Ginkgo biloba* has no discernable benefits on cognition in either patients with AD, in preventing AD, or in the healthy elderly. The clinical implications of this conclusion are that *Ginkgo biloba* should not be recommended to healthy elderly or patients with AD. The authors themselves make assumptions about the criteria suggested in this article (which are the generally accepted standards by both U.S. and European regulatory agencies for clinical research) used to judge studies. A second and related question is whether the evidence regarding ginkgo on cognition is sufficient to conclude that the compound is not effective, and further research is unlikely to change this conclusion and therefore not necessary. In summary the authors would suggest that if *Ginkgo biloba* had to meet present regulatory guidelines to be marketed, it would be with drawn from development.

Lüders *et al.* (2012) summarised the increasing knowledge that has been obtained from clinical studies about the impact that vascular factors have on cognitive function and dementia (vascular dementia). Due to demographic reasons and still insufficient control of all vascular risk factors, dementia and associated problems are of increasing importance and will have impact on economical and social develpoment in most countries. The incidence of cognitive impairment and dementia will increase exponentially. As long as no causal therapy for dementia exists, diagnosis and control of risk factors for dementia will need much more attention. Hypertension is not only the most important risk factor for stroke that often leads to dementia but also for silent brain infarcts, which are also associated with onset of dementia. Uncontrolled hypertension is associated with cognitive impairment and sufficient control of hypertension in middle-aged patients can reduce the risk of dementia in older ages. Nevertheless, treatment of all other risk factors, such as diabetes mellitus, smoking, hyperlipidemia, aterial fibrillation, is important to reduce the onset of not only vascular but also Alzheimer dementia.

Healthy participants:

Study	**Trick *et al.* 2004**	
Indication	To investigate the effects of continuing treatment with *Ginkgo biloba* extract (GBE) on the ADL and mood	
Treatment duration	4 months pretreatment; 6 months follow-up (study period)	
Test product	LI 1370	
Single / Daily dosage	120 mg/120 mg	
Study design	randomised	no
	double-blind	no
	controlled	yes (no treatment: NT)
	parallel group	yes
	multicentre	-
	number of patients	1570; 4 groups: GBE-GBE (111), GBE-NT (314), NT-BGE (407) and NT-NT (738)
	age	>60 years
	wash-out	no
Outcome	There were significant differences in the mean overall line analogue rating scale (LARS) and self-rating activities of daily living scale (SR-ADL) scores between the four treatment combination groups at the end of the follow-up period. A factor analysis of the LARS revealed two factors, “mood” and “alertness”. When scores from each of the treatment groups were examined over the whole 10 month period it was evident that the ratings of overall competence in the SR-ADL and both factors of the LARS were diminished on the cessation of treatment with LI 1370, and improved when	

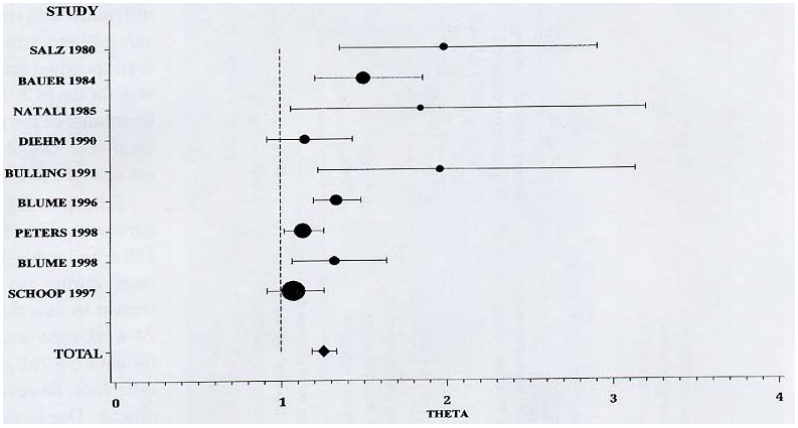
	LI 1370 treatment was initiated. The magnitude of the improvement on all scales was revealed to the overall duration of LI 1370 supplementation. Author's conclusion: Significant differences between the groups of subjects treated with LI 1370 for different periods of time (4-10 months) suggests that the extract has a demonstrable effect in improving mood and the self-assessed performance of the tasks of everyday living.

4.2.2.2. Peripheral arterial occlusive disease (intermittent claudication)

Reviews and meta-analyses:

Horsch and Walther (2004) stated in a review that in the majority of the studies there was an advantage of EGb 761 in the increase of pain-free walking distance compared to placebo. For 7 studies, the advantage was found to be statistically significant. Testing the relevant superiority showed a significant result in 6 of the selected 9 studies. The pooled estimator of the ratio amounts to θ=1.23 (95% CI: 1.16, 1.31) and demonstrates the efficacy of EGb 761 over placebo as well.

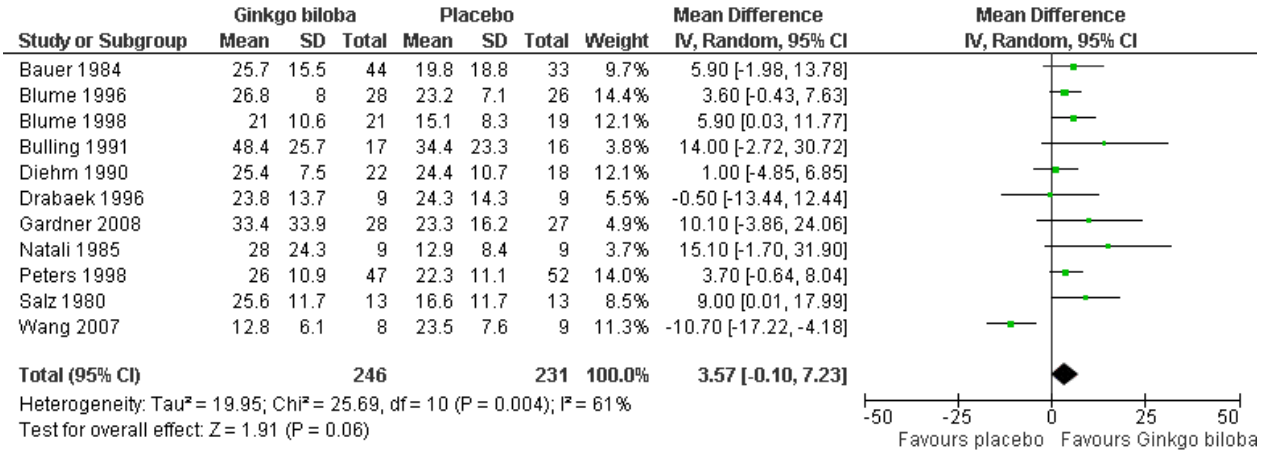
Ratio theta of the increase in pain-free walking distance under EGb 761 and placebo with 95% CI (theta >1 means superiority of EGb 761; Horsch and Walther 2004).



Author's conclusion: The reviewed studies confirm the efficacy of EGb 761. In 6 of 9 studies, a relevant superiority compared to placebo could be demonstrated. The pooled evaluation of all studies showed the clinical relevance of the therapeutic effects of EGb 761 as well. With a good to very good tolerability, the benefit/risk ratio is consequently in favour of a therapy with EGb 761 in patients with PAOD stage II (according to Fontaine).

Nicolaï *et al.* 2009: In the abstract of the Cochrane Review on "*Ginkgo biloba* for intermittent claudication (Review)" the results are as follows: Fourteen trials with a total of 739 participants were included. Eleven trials involving 477 participants compared *Ginkgo biloba* with placebo and assessed the absolute claudication distance. Following treatment with *Ginkgo biloba* at the end of the study the absolute claudication distance increased with an overall effect size of 3.57 kilocalories (CI -0.10 to 7.23, p=0.06), compared with placebo. This translates to an increase of just 64.5 (CI -1.8 to 130.7) meters on a flat treadmill with an average speed of 3.2 km/h. Publication bias leading to missing data or "negative" trials is likely to have inflated the effect size.

Forest plot of clinical studies comparing the absolute claudication distance (expressed as kilocalories) at the end of the study



Author's conclusion: There is no evidence that *Ginkgo biloba* has a clinically significant benefit for patients with PAD.

Pittler and Ernst (2000) included eight randomised, placebo-controlled, double-blind trials in a meta-analysis. In three of these trials EGb 761 was applied. There is no concrete information on the other extracts. A significant difference in the increase in pain-free walking distance in favour of *Ginkgo biloba* (weighed mean difference: 34 meters, 95% confidence interval [CI]: 26 to 43 meters) was determined. In studies using similar methodological features (ergometer speed: 3 km/h, inclination: 12%) this difference was 33 meters in favour of *Ginkgo biloba* (95% CI: 22 to 43 meters). Concerning to the authors these results suggest that *Ginkgo biloba* extract is superior to placebo in the symptomatic treatment of intermittent claudication. However, the size of the overall treatment effect is modest and of uncertain clinical relevance.

Letzel and Schoop (1992): Clinical trials on the efficacy of EGb 761 and pentoxifylline were assessed. On average an increase of 45% (EGb 761) or 57% (pentoxifylline) in relation to initial values was found.

Study	**Gardner *et al.* 2008**	
Indication	Claudication symptoms of peripheral artery disease	
Treatment duration	4 months	
Test product	EGb 761	
Single / Daily dosage	60 mg/300 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	-
	number of patients	62
	age	70±8 years (mean±SD)
	wash-out	at least one month
Outcome	Maximal treadmill walking time increased by 20±80 and 91±242 seconds in the placebo and the EGb 761 groups, respectively (p=0.12). Pain-free walking time increased by 15±31 and 21±43 seconds, respectively (p=0.28). No significant differences were detected between groups for any of the secondary outcomes.	

	Author's conclusion: In older adults with PAD, *Ginkgo biloba* produced a modest but insignificant increase in maximal treadmill walking time and flow-mediated vasodilation. These data do not support the use of *Ginkgo biloba* as an effective therapy for PAD, although a longer duration of use should be considered in any future trials.

Study	**Thomson *et al.* 1990**	
Indication	Fontaine stage 2 peripheral vascular disease	
Treatment duration	24 weeks	
Test product	EGb 761 (Tanakan)	
Single / Daily dosage	Three tablets daily	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	37; 20 (EGb 761), 17 (placebo)
	age	-
	wash-out	6 weeks
Outcome	Severity of pain using a 10 cm linear analogue scale was significantly improved in the EGb 761 group, but not in the placebo group. Claudication distance increased significantly by EGb 761, but not in the placebo group. A/B ratio and Doppler ankle responses to exercise did not show any significant change in either group, nor did the post exercise recovery time. Author's conclusion: EGb 761 is a safe and effective method of improving walking distance and reducing pain severity in patients with intermittent claudication, although Doppler studies have failed to suggest any gross improvement in the perfusion of the ischaemic leg.	

Study	**Wang *et al.* 2007**	
Indication	PAD	
Treatment duration	24 weeks	
Test product	*Ginkgo biloba* tablets	
Single / Daily dosage	120 mg/240 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (controlled)
	parallel group	yes
	multicentre	-
	number of patients	17; 8 (ginkgo), 9 (placebo)
	age	50-80 years
	wash-out	-
Outcome	Of the measured variables only the maximal walking time increased significantly in the ginkgo group after the combined treatment of *Ginkgo biloba* tablets and exercise training (from 236±112 seconds to 557±130 seconds, p=0.001). Similar change was also found in the placebo	

	group after exercise training (from 384±125 seconds to 820±146 seconds, p=0.001). Author's conclusion: Supervise exercise training combined with *Ginkgo biloba* treatment did not produce greater beneficial effects than exercise training alone in patients with PAD.

Study	**Wu *et al.* 2007**	
Indication	Coronary artery disease (CAD)	
Treatment duration	one-time administration	
Test product	*Ginkgo biloba* extract (GBE) injectable solution (Ginaton, manufactured in China)	
Single / Daily dosage	intravenous 0.7 mg/min GBE for 120 min	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	80; 42 (GBE), 38 (placebo)
	age	62±12 years (GBE), 58±13 years (placebo)
	wash-out	-
Outcome	GBE significantly increased distal left anterior descending coronary artery (LAD) blood flow in maximal diastolic peak velocity (MDPV), maximal systolic peak velocity (MSPV) and diastolic time velocity integral (DTVI) compared with the control group (16.14±10.93% vs. 0.28±2.14%, 9.14±8.23% vs. 0.79±2.56%, and 15.23±7.28% vs. 0.42±2.43%, respectively, p<0.01). Increased brachial artery flow-mediated dilation (FMD) by 69.75% (from 3.95±1.49% to 6.55±2.51%, p<0.01). A linear correlation was found between the percentage changes in MDPV, MSPV, or DTVI of LAD blood flow and the percentage change in brachial artery FMD following treatment with GBE (r=0.612, 0.486, or 0.521, respectively, p<0.01). Author's conclusion: GBE treatment in CAD patients leads to an increase of LAD blood flow in MDPV, MSPV and DTVI. The increased response might relate to the improved endothelium-dependent vasodilatory capacity.	

Healthy participants:

Study	**Galduróz *et al.* 2007**	
Indication	To compare the effects of age and gender on blood viscosity and to appraise the effectiveness of *Ginkgo biloba* extract in reducing blood viscosity	
Treatment duration	6 months	
Test product	EGb 761 (produced by Maze Productos Quimicos e Farmaceuticos Ltda. and prepared by Magister Medicamentos Ltda.)	
Single / Daily dosage	80 mg/80 mg	
Study design	randomised	yes

	double-blind	-
	controlled	yes (placebo and Allium sativum)
	parallel group	-
	multicentre	no
	number of patients	Stage 1: 80 male and 80 female; Stage 2: 60 male; Stage 3: 25 male
	age	Stage 1: 80 aged 18-60 and 80 aged ≥61 (same age profile for male and female)
	wash-out	-
Outcome	Significant differences were found when considering age; measures of blood viscosity in the younger group was significantly lower than in the senior group; in both groups (3.79±0.07 and 4.19±0.3, younger and older males, respectively; $p<0.01$; and 3.37±0.3 and 4.36±0.3, young and old females, respectively; $p<0.001$). Comparing the measured blood viscosity of the younger men and women, a significant difference was found (3.79±0.07 and 3.37±0.3, men and women, respectively; $p<0.01$), whereas no significant difference was found in the older group (4.19±0.3 and 4.36±0.3, men and women, respectively; $p=0.2$). Also found was a positive correlation between age and blood viscosity ($r=0.32$; $p<0.05$), with viscosity increasing with age. EGb 761 led to the highest reduction in blood viscosity compared with placebo and A. sativum. In relation to the use of the two substances, *Ginkgo biloba* and A. sativum, dry extract of *Ginkgo biloba* proved to be more effective in reducing blood viscosity.	

Study	**Wu *et al.* 2008**	
Indication	To test the effects of *Ginkgo biloba* extract (GBE) on LAD blood flow and endothelium-dependent brachial artery FMD	
Treatment duration	one-time administration	
Test product	GBE injectable solution (Ginaton, manufactured in China)	
Single / Daily dosage	intravenous 0.7 mg/min GBE for 120 min	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	60; 30 (GBE), 30 (placebo)
	age	54±10 years (GBE), 56±8 years (placebo)
	wash-out	-
Outcome	GBE significantly increased LAD blood flow in MDPV, MSPV and DTVI compared with the placebo group (19.16±13.91% vs. 0.30±2.55%, 17.76±14.56% vs. 0.53±2.32%, and 21.73±16.13% vs. 0.81±2.33%, MDPV, MSPV, and DTVI improvement from baseline, respectively, $p<0.01$).Brachial artery FMD was also increased by 56.03% (from 7.21±2.52% to 11.28±3.95%, $p<0.01$). A linear correlation was found between the percentage change in MDPV, MSPV, or DTVI of LAD blood flow and the percentage change in brachial artery FMD following treatment with GBE ($r=0.538$, 0.366, or 0.573, respectively, $p<0.01$, $p<0.05$, or $p<0.01$).	

	Author's conclusion: GBE treatment in healthy elderly adults leads to the increase of LAD blood flow in MDPV, MSPV and DTVI, and the increased response might relate to the improved endothelium-dependent vasodilatory capacity.

4.2.2.3. Adjuvant therapy in tinnitus of vascular and involutive origin

Study	**Drew and Davies 2001**	
Indication	Tinnitus that was comparatively stable	
Treatment duration	12 weeks	
Test product	LI 1370	
Single / Daily dosage	50 mg/150 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	-
	number of patients	1121; 978 were matched (489 pairs)
	age	18-70 years
	wash-out	-
Outcome	There were no significant differences in primary or secondary outcome measures between the groups. 34 of 360 participants receiving active treatment reported that their tinnitus was less troublesome after 12 weeks of treatment compared with 35 of 360 participants who took placebo. Author's conclusion: 50 mg *Ginkgo biloba* extract LI 1370 given 3 times daily for 12 weeks is no more effective than placebo in treating tinnitus.	

Study	**Holgers *et al.* 1994** (only the second part is stated below)	
Indication	Persistent severe tinnitus	
Treatment duration	2 weeks	
Test product	*Ginkgo biloba* extract (GBE) (Seredrin, Farmaflor)	
Single / Daily dosage	14.6 mg/29.2 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	no (but crossover)
	multicentre	-
	number of patients	20
	age	41-77 years
	wash-out	1 week (between crossover application)
Outcome	Statistical group analysis gives no support to the hypothesis that GBE treatment has any effect on tinnitus, although it is possible that GBE has an effect on some patients due to several reasons, e.g. the diverse etiology of tinnitus.	

Study	**Morgenstern and Biermann 2002**	
Indication	Chronic tinnitus aurium	
Treatment duration	12 weeks (open 10-day EGb 761 infusion pretreatment)	
Test product	EGb 761	
Single / Daily dosage	80 mg/160 mg (pretreatment: 1 infusion (200 mg)/day)	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	yes
	multicentre	-
	number of patients	60
	age	median age: 45 (EGb 761), 47 (placebo)
	wash-out	-
Outcome	For the primary outcome measure, significant superiority of EGb 761 over placebo was demonstrated in the ITT analysis data set after 4, 8 and 12 weeks of out-patient treatment ($p<0.05$, 1-tailed), although the absolute treatment group difference was moderate. The results were supported by the secondary outcome measures for efficacy (e.g. decreased hearing loss, improved self-assessment of subjective impairment). During out-patient treatment, there were no adverse events under EGb 761. Author's conclusion: A combination of infusion therapy followed by oral administration of EGb 761 appears to be effective and safe in alleviating the symptoms associated with tinnitus aurium.	

Study	**Halama *et al.* 1988**	
Indication	Mild to medium cerebrovascular insufficiency	
Treatment duration	12 weeks	
Test product	EGb 761	
Single / Daily dosage	40 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	no
	number of patients	40
	age	55-85 years
	wash-out	-
Outcome	The symptom of tinnitus was specifically asked for and their specification was documented with the aid of a four-stage rating scale. In the group receiving active substance superior effect was shown in the symptom of tinnitus ($p=0.035$).	

Reviews and meta-analyses:

Von Boetticher (2011) concluded that EGb 761, a standardised *Ginkgo biloba* extract, is an evidenced-based treatment option in tinnitus.

Rejali *et al.* (2004): In the review it was concluded that there is now level 1a evidence that *Ginkgo biloba* does not benefit patients with tinnitus.

Hilton and Stuart (2010): The author's conclusion in the abstract in the Cochrane review "*Ginkgo biloba* for tinnitus" is: The limited evidence did not demonstrate that *Ginkgo biloba* was effective for tinnitus which is a primary complaint. There was no reliable evidence to address the question of whether *Ginkgo biloba* is effective for tinnitus associated with cerebral insufficiency.

Smith *et al.* (2005) concluded in the review: Although there are some clinical trials that have yielded positive results from the use of *Ginkgo biloba* extracts (…), these studies are few and have been limited either by design flaws (…), the small size of the significant effect (…), or else the results have not been published in peer-reviewed journals (…) and therefore the quality of the research is not proven. On the other hand, the two most systematic clinical trials, both of which are double-blind and placebo-controlled, and are published in respected peer-reviewed journals, have yielded negative results and suggest that *Ginkgo biloba* extracts are of little more use in the treatment of tinnitus than placebo. This is an important conclusion because treatments that do not have therapeutic efficacy not only waste money but can prevent patients from seeking therapy that is efficacious. … Furthermore, the unsupervised use of *Ginkgo biloba* extracts with other medications could lead to adverse side effects (e.g. haemorrhagic effects of concurrent use of aspirin) which are unnecessary and not justified in terms of therapeutic benefit.

4.2.2.4. Vertigo

Study	**Issing *et al.* 2005**	
Indication	Atherosclerosis-related vertigo	
Treatment duration	8 weeks	
Test product	standardised *Ginkgo biloba* extract	
Single / Daily dosage	40 mg/120 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (vertigoheel)
	parallel group	yes
	multicentre	n=13
	number of patients	170; 87 (vertigoheel), 83 (ginkgo)
	age	60-80 years
	wash-out	-
Outcome	Both treatments improved vertigo status. From a baseline mean value of 26.1±5.2 (on a 50-point scale) in the Vertigoheel group, the dizziness questionnaire score improved by -10.6±10.0, and by -10.7±9.0 from 25.8±4.7 in the *Ginkgo biloba* group. Statistical analysis of this endpoint showed that Vertigoheel was not inferior to *Ginkgo biloba*. The 95% CI for the difference between treatment did not reach the inferiority threshold of 0.36 at any of the time points tested. The results were supported by the results of a line walking test, Unterberger´s stepping test, and patient and physician global assessments of therapeutic effect. Both treatments were well tolerated. Author's conclusion: Vertigoheel is an appealing alternative to established *Ginkgo biloba* therapy for atherosclerosis-related vertigo.	

Study	**Haguenauer *et al.* 1986**	
Indication	Vertiginous syndrome of recent onset and undetermined origin	
Treatment duration	3 months	
Test product	EGb 761	
Single / Daily dosage	80 mg/160 mg	
Study design	randomised	yes
	double-blind	yes
	controlled	yes (placebo)
	parallel group	-
	multicentre	n=3
	number of patients	67; 34 (EGb 761), 33 (placebo)
	age	52±2.5 (EGb 761), 46.4±2.4 (placebo)
	wash-out	-
Outcome	The results show that effectiveness of *Ginkgo biloba* extract on the intensity, frequency, and duration of the vertigo was statistically significant. At the end of the trial, 47% of the treated patients were free of their symptoms, as against 18% of those who received placebo (student t-test: $p<0.05$).	

Reviews and meta-analyses:

Hamann (2007): The results in the review show a beneficial effect of EGb 761 on vestibular compensation that has been demonstrated in preclinical and clinical studies. In conclusion, evidence of the efficacy of EGb 761 for the treatment of vertiginous syndromes is presented in the available studies.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

Most of the studies mentioned in the chapter “Clinical Data” are conducted in elderly due to the range of indications of medicinal products containing *Ginkgo biloba*. Only a few studies were conducted in patients under the age of 18 years. Some of these studies are listed in the following.

Donfrancesco and Ferrante (2007) collected preliminary information on the possible efficacy and tolerability of EGb 761 as a treatment of dyslexia in school-aged children. 15 children aged between 5 and 16 years with dyslexia participated in an open-label trial of EGb 761 given as a single dose of 80 mg in the morning. Standardised tests for dyslexia were administered at baseline and at the end of the study. All children completed the trial. The score of the standardised tests for dyslexia decreased. On the list of words the score decreased from mean 4.33 (SD=2.37) at baseline to 2.66 (SD=1.58) at the end of the study ($p<0.01$), on the list of non-words from mean 3.39 (SD=1.5) at baseline to 2.26 (SD=0.92) at the end of the study ($p<0.02$) and on the reading piece from mean 3.52 (SD=2.11) to 2.13 (SD=1.25) at the end of the study ($p<0.05$). At the end of the study 9 children did not perform below the -2 SD on the list of words and 7 on reading text and so they no longer fulfilled the DSM-IV-TR criteria for dyslexia. A brief period of headache was reported by the parents of two children.

Szczurko *et al.* (2011): A pilot clinical trial concerning vitiligo vulgaris was performed in 12 participants aged 12-35 years (8 participants under 18). Patients received 60 mg of *Ginkgo biloba* (standardised to 15 mg (25%) ginkgoflavonglycosides and 4 mg (6.67 %) terpene lactones per pill, manufactured by Seroyal) two times per day for 12 weeks. Effectiveness was assessed using the Vitiligo Area Scoring Index (VASI) and the Vitiligo European Task Force (VETF), which are measures evaluating the extent of depigmentation and the area of vitiligo lesions, staging, and disease activity,

respectively. The total VASI score improved by 0.5 (p=0.021) from 5.0 to 4.5, which indicated an average repigmentation of vitiligo lesions of 15%. The progression of vitiligo stopped in all participants. VETF total vitiligo lesion area decreased 0.4% (p=0.102) from 5.9 to 5.6 from baseline to week 12. VETF staging score improved by 0.7 (p=0.10) from 6.6 to 5.8, and the VETF spreading score improved by 3.9 (p<0.001) from 2.7 to -1.2. There were no statistically significant changes in safety assessed by serum coagulation factors (platelets, PTT, INR).

Esposito and Carotenuto (2011): The study has investigated administration of ginkgolide B as preventive treatment in primary headache in young patients. Ginkgolide B was considered as a pharmacological aid for the treatment of migraine in adult patients because its peculiar modulation of the glutamatergic transmission in the CNS and on platelet activating factor (PAF). 119 school-aged patients (mean age 9.7±1.42) received ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium complex (not further specified) twice a day for 3 months. At the end of the study the mean frequency per month of migraine was significantly decreased (9.71±4.33 vs. 4.53±3.96 attacks; p<0.001).

Usai (2011): Another study investigated the effect of ginkgolide B as preventive treatment to confirm the long-term utility on a group of young patients suffering from primary headache such as migraine without aura. In an open-label trial 30 patients aged between 8 and 18 (mean age 13.5±2.2) were treated orally with a combination of ginkgolide B 80 mg, coenzyme Q10 20 mg, vitamin B2 1.6 mg and magnesium 300 mg twice per day for 3 months. The number of monthly migraine attacks was reduced after 3 months of treatment in relation to pre study baseline. At 1-year follow-up mean number of days of headaches per month decreased significantly from 7.2±4.3 to 1.6±1.7 (p 0.000).

Cala *et al.* (2003) examined the use of herbal therapy in children or adolescents receiving care for a depressive disorder or Attention-Deficit-Hyperactivity Disorder (ADHD) (with or without comorbidities). The main outcome measure was primary caregivers´ self-report of the use of herbal therapy in their children using a 23-item questionnaire on 117 parents or caregivers´ of patients younger than 18 years (mean age 10.9±3.1 years). The mean age at onset of a psychiatric condition was 8.1±3.3 years. 110 patients (94.0%) were being treated with prescription drugs at the time of the study. The overall lifetime prevalence of herbal therapy in patients was 23 (19.6%) of the 117 patients. Recommendations from a friend or relative resulted in the administration of herbal medicines by 61% of 23 caregivers. No caregivers reported that a recommendation from a health care professional or that an adverse effect from conventional drug was the primary reason herbal therapy was tried in their children. Herbal medicines were given most frequently for a behavioural condition as reported by 8 of 23 caregivers, with *Ginkgo biloba* (not further specified) most prevalent (26%). 15 caregivers (65%) of 23 who gave their children herbal medicines thought they were effective, and of these, all perceived herbal therapy to be at least somewhat if not very effective. None of the 23 caregivers reported any adverse effects in their children from herbal medicines. However, decreased effectiveness or ineffectiveness was the most common reported reason for stopping herbal therapy.

Salehi *et al.* (2010) evaluated their hypothesis that *Ginkgo biloba* would be beneficial for treatment of Attention-Deficit-Hyperactivity Disorder (ADHD) in a randomised, double-blind, parallel group comparison of *Ginkgo biloba* (Ginko T.D. Tolidaru, Iran) and methylphenidate. Fifty outpatients (39 boys and 11 girls) aged between 6-14 years with DSM-IV-TR diagnosis of ADHD were randomly assigned to receive treatment using tablet of ginkgo T.D. at a dose of 80-120 mg/day depending on weight (80 mg/day for <30 kg and 120 mg/day for >30 kg) (group 1) or methylphenidate at a dose of 20-30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg) (group) for 6 weeks. The principal measure of outcome was the Teacher and Parent ADHD Rating Scale-IV. Patients were assessed at baseline and at 21 and 42 days of treatment. Significant differences were observed between the two groups. The changes at the end of the studycompared to baseline were: -6.52±11.43 (mean±SD) and -15.92±11.44 (mean±SD) for Ginko T.D. and methylphenidate,

respectively for Parent ADHD Rating Scale. The changes at the endpoint compared to baseline were: -0.84±6.79 (mean±SD) and -14.04±8.67 (mean±SD) for Ginko T.D. and methylphenidate, respectively for Teacher ADHD Rating Scale. The difference between the two groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group.

Biggs *et al.* (2010): In a secondary analysis of the Ginkgo Evaluation of Memory (GEM) study *Ginkgo biloba* and risk of cancer was analysed. Evidence from *in vitro* and *in vivo* studies suggests that *Ginkgo biloba* has cancer chemopreventive properties, but epidemiological evidence is sparse. 3069 subjects (≥75 years) participated in the GEM study which had a randomised, double-blind and placebo-controlled design. Participants received 120 mg EGb 761 two times daily or placebo. The results show there were 148 cancer hospitalisations in the placebo group and 162 in the EGb 761 group (HR, 1.09; 95% CI, 0.87-1.36; p=0.46). Among the site-specific cancers analysed, we observed an increased risk of breast (HR, 2.15; 95% CI, 0.97-4.80; p=0.06) and colorectal (HR, 1.62; 95% CI, 0.92-2.87; p=0.10) cancer, and a reduced risk of prostate cancer (HR, 0.71; 95% CI, 0.43-1.17; p=0.18). In conclusion, these results do not support the hypothesis that regular use of *Ginkgo biloba* reduces the risk of cancer.

4.3. Overall conclusions on clinical pharmacology and efficacy

Clinical pharmacology

In clinical studies pharmacodynamic effects on brain function, memory and blood flow were mentioned in healthy subjects. Chronic treatment with *Ginkgo biloba* resulted in an improvement of cognitive deficits in older subjects, whereas in young subjects there were no effects. The exact mechanism is not known. Human pharmacologiacal 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.

The examined coadministration of *Ginkgo biloba* with aspirin, warfarin and antipyrine revealed no pharmacodynamic interactions. However, the combination of *Ginkgo biloba* and cilostazol caused prolongation of bleeding time without enhancing antiplatelet activity, thus increasing the risk of haemorrhage.

Pharmacokinetic parameters show a high bioavailability of terpene lactones given as a solution (80% for ginkgolide A, 88% for ginkgolide B and 79% for bilobalide). 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-lifes of ginkgolide A and 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 9-11 hours and for bilobalide 3-4 hours.

A lot of clinical pharmacokinetic interaction studies were conducted in which an interaction potential of *Ginkgo biloba* extract with other medicinal products and an effect on drug metabolising enzymes was supposed. The influence of *Ginkgo biloba* on drug metabolising CYPs has been demonstrated with various probe substrates for the corresponding CYPs. Both, an inducing and an inhibitory effect were suggested for *Ginkgo biloba* on CYP3A4 by results of interaction studies, depending on the study design. Whereas a daily dose of 240 mg EGb 761 and extracts other than EGb 761 supposed an inducing effect, a higher daily dose of EGb 761 assumed an inhibitory effect. An induction of CYP2C9

was assumed at a daily dose of 360 mg of EGb 761. Also inducing effects for *Ginkgo biloba* extracts other than EGb 761 on CYP2C19 were observed.

The inhibitory effect of *Ginkgo biloba* extract on the pharmacokinetics of the P-gp substrate talinolol was studied in healthy volunteers. The observed increase of C_{max} by 33% and AUC by 21% without any significant alterations in T_{max} and $T_{1/2}$ of talinolol supports the hypothesis of Blonk et al. (2012): that a possible explanation for the increase in C_{max} and bioavailability of a drug when combined with EGb 761 could be the inhibition of P-gp by EGb 761. These findings could also be a reflection of individual variation in the inhibitory potential of P-gp by *Ginkgo biloba*. The expression and transport activities may differ between individuals due to genetic variation in the highly polymorphic MDR1 gene. Therefore, the extent of the inhibition of P-gp may vary accordingly.

One study examining clinical pharmacokinetic interactions of *Ginkgo biloba* extract and nifedipine, a calcium-channel blocker, indicated individual increase in C_{max} by concomitant administration. The two subjects had severer and longer-lasting headaches with dizziness or hot flushes in combination.

From two reviews clinical pharmacological interactions of *Ginkgo biloba* with alprazolam, haloperidol, trazodone, omeprazole, aspirin, ibuprofen, nifedipine, warfarin, antiepileptics, antidiabetics, diuretics and nonsteroidal anti-inflammatory drugs were mentioned.

Clinical efficacy

The EMA “Guideline on Medicinal Products for the Treatment of Alzheimer’s Disease and Other Dementias” (2009) focuses on the development of new medicinal products for the treatment of dementia and its subtypes. Other guidelines focus more on clinical aspects and care of people with dementia. Recommendations from the article “Management of dementing disorders, conclusions from the Canadian consensus conference on dementia (1999)” have been developed with particular attention to the context of primary care, and are intended to support family physicians in their ongoing assessment and care of patients with dementia. Also the German guideline on dementia (S3-Leitlinie “Demenzen” [2009]) gives statements to prevention, diagnostic and therapy of dementia as well as to mild cognitive impairment. The aim is to give assistance to persons who treat and care patients with dementia and their relatives in decision making of diagnostic, therapy, care and consultation. Besides pharmacological therapy special emphasis was placed on psychosocial intervention. A British National Institute for Health and Clinical Excellence (NICE) guideline “dementia” (2012) makes recommendations for the identification, treatment and care of people with dementia and the support of carers. Settings relevant to these processes include primary and secondary healthcare, and social care. In addition the Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline “Management of patients with dementia” (2006). It covers also diagnosis, non-pharmacological interventions, and pharmacological interventions in people with dementia. The obligation for medicinal products with indications in the field of neurological disorders to apply for a marketing authorisation via the centralised procedure is addressing new substances.

The results of the IQWIG report 2008 support the use of ginkgo containing products in patients with mild, moderate, or severe dementia, which includes AD and mixed-type dementia (AD and VaD). The following studies were analysed in the report: Schwabe (2008), Napryeyenko and Borzenko (2007), Yancheva *et al.* (2006), Schneider *et al.* (2005), LeBars *et al.* (1997), Kanowski *et al.* (1996), Digger (2007). It was evidenced that 240 mg ginkgo extract EGb 761 has a benefit on “activities of daily living”. Further, hints of a benefit on “cognitive function” and “general psychopathological symptoms” are mentioned. However, the conclusion that ginkgo has a beneficial effect is based on very heterogeneous results. Therefore no summarising conclusion was made on the potential effect size. Additionally there is a sign that this benefit is only present in patients with accompanying psychopathological symptoms. Moreover, it needs to be considered that results were strongly affected

by 2 studies conducted in an Eastern European health-care setting with specific patient populations (among other things, patients with a high rate of accompanying psychopathological symptoms). Meanwhile two recent studies are published by Herrschaft *et al.* (2012) and Ihl *et al.* (2010) that are supportive for the monograph relevant indication as well. These studies include patients with mild to moderate dementia (AD or VaD) with neuropsychiatric symptoms.

According to the complexity of the disease partial aspects should be considered in the therapeutical concept of dementia. Besides others the factor “quality of life” of patients and caregivers should be included in these considerations. The IQWIG report 2008 and two more recent studies (Grass-Kapanke *et al.* (2011) and Heinen-Kammerer *et al.* (2005)) addressed this parameter of improving the patient’s and caregiver’s condition.

On the part of the EMA it is noticed that the “Guideline on Medicinal Products for the Treatment of Alzheimer’s Disease and Other Dementias” is under discussion (“Concept paper on no need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias”). It is said in the guideline, that despite the rapid progress in understanding of the neurobiology and pathophysiology of AD, the most common form of dementia, only cholinesterase-inhibitors and memantine have been approved for the symptomatic treatment with overall limited clinical improvement and no product has been approved for disease modification in any neurodegenerative disorder. Furthermore, it is stated that new diagnostic criteria and choice of outcome parameters should be revised according to the complex pathomechanism of dementia diseases.

Also the long standing use with ginkgo containg products should be kept in mind.

In summary, clinical trials investigating indications in the therapeutic area of tinnitus and claudication intermittens are not convincing to support well-established use of this application. There are appropriate studies which support the usage of *Ginkgo biloba* preparations in the therapeutic area of mild dementia demonstrating improvement of cognitive impairment and of quality of life. The most relevant clinical trials have been performed including patients of 50 years and above. The data particularly indicate that improvements were observed in patients with neuropsychiatric diagnostics.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

See section 4.1. and 4.2.

Furthermore, as reviewed by **Oberpichler-Schwenk (1995)** no case of overdose has been reported so far. The available data prove a low toxicity of *Ginkgo biloba* extract, whereby it should be keep in mind that these toxicological data were identified with the special extract EGb 761.

5.2. Patient exposure

According to the “Arzneiverordungs-Report 2012” (published by U. Schwabe and D. Paffrath) the long lasting effect of prescription decline of *Ginkgo biloba* preparations continued onwards in 2011. In 2011 the prescribed daily doses dropped by 8.8% to 5.5 Mio. compared to the year 2010.

5.3. Adverse events and serious adverse events and deaths

Adverse events

In the WEU part of the monograph, the given frequencies of adverse events were pooled and estimated from the above-mentioned clinical trials (see section 4.2.). No assessment of the quality of

studies regarding adverse event reporting was done. Only those trials which mentioned the specific adverse event have been considered when calculating the frequencies. A frequency calculation was performed for the most reported adverse events which are: headache, dizziness, respiratory tract infection, hypertension/blood pressure increased, gastrointestinal complaints (diarrhoea, abdominal pain and nausea), angina pectoris and tinnitus. It should be keep in mind that the adverse events profiles for the Ginkgo extract preparations and placebo groups were similar or even higher rates exist in the placebo group.

For the adverse events mentioned in the monograph in the traditional use part, data based on information of the extract are given. There are no reports of adverse events regarding the traditionally used powder. Therefore the possible adverse events are transferred from the WEU part without the given frequencies.

In Germany currently (June 20, 2012) over 400 adverse reactions reports in nearly all organ systems are labelled according to the **Federal Institute for Drugs and Medical devices (BfArM) database for adverse events**. The following adverse events were most frequently mentioned (more than 20 reports for each adverse event): dizziness, headache, pruritus, vomiting, nausea, diarrhoea, chills, rash and erythema.

Snitz *et al.* (2009) stated in their analyses of the GEM study: The adverse event profiles for the *Ginkgo biloba* and placebo groups were similar and the rates of serious adverse events, including mortality and incidence of coronary heart disease, stroke of any type, and major bleeding, did not differ significantly.

Kuller *et al.* (2010): In the GEM study cardiovascular disease (CVD) was a secondary outcome. The identification and classification of CVD was based on methods used in the Cardiovascular Health Study. Differences in time to event between *Ginkgo biloba* and placebo were evaluated using Cox proportional hazards regression adjusted for age and sex. There were 355 deaths in the study, 87 due to coronary heart disease with no differences between *Ginkgo biloba* and placebo. There were no differences in incident myocardial infarction (n=164), angina pectoris (n=207), or stroke (151) between *Ginkgo biloba* and placebo. There were 24 haemorrhagic strokes, 16 on *Ginkgo biloba* and 8 on placebo (not significant). There were only 35 peripheral vascular disease events, 12 (0.8%) on *Ginkgo biloba* and 23 (1.5%) on placebo (p=0.004, exact test). Most of the peripheral vascular disease cases had either vascular surgery or amputation. In conclusion, there was no evidence that *Ginkgo biloba* reduced total or CVD mortality or CVD events. There were more peripheral vascular disease events in the placebo arm. *Ginkgo biloba* cannot be recommended for preventing CVD. Further clinical trials of peripheral vascular disease outcomes might be indicated.

DeKosky *et al.* (2008): Secondary objectives in the GEM study were to evaluate the effect of *Ginkgo biloba* among other things on total mortality and incidence of cardiovascular disease (CVD) (defined as the combined incidence of confirmed coronary heart disease, angina, stroke, transient ischemic attack, coronary artery bypass surgery, or angioplasty; incidence was confirmed by review of the participant's medical record after self-report). There were 379 deaths from any cause. The adverse event profiles for EGb 761 and placebo were similar and there were no statistically significant differences in the rate of serious adverse events. The mortality rate was similar in the 2 treatment groups (HR, 1.04; 95% CI, 0.85-1.26; p=0.72). There were no differences in the incidence of coronary heart disease (myocardial infarction, angina, angioplasty, or coronary artery bypass graft) or stroke of any type by treatment group. Of particular note rates of major bleeding did not differ between the treatment groups (HR, 0.97; 95% CI, 0.77-1.23; p=0.81), and bleeding incidence did not differ for individuals taking aspirin and assigned to either EGb 761 or placebo (rates of 1.98 and 1.76 per 100 person-years, respectively, p=0.44). Although there were twice as many haemorrhagic strokes in the EGb 761 group compared with the placebo group (16 vs. 8), the number of cases was small and nonsignificant in the analysis.

Biggs *et al.* (2010): In a secondary analysis of the Ginkgo Evaluation of Memory (GEM) study *Ginkgo biloba* and risk of cancer was analysed. Evidence from *in vitro* and *in vivo* studies suggests that *Ginkgo biloba* has cancer chemopreventive properties, but epidemiological evidence is sparse. 3069 subjects (≥75 years) participated in the GEM study which had a randomised, double-blind and placebo-controlled design. Participants received 120 mg EGb 761 two times daily or placebo. The results show there were 148 cancer hospitalisations in the placebo group and 162 in the EGb 761 group (HR, 1.09; 95% CI, 0.87-1.36; p=0.46). Among the site-specific cancers analysed, we observed an increased risk of breast (HR, 2.15; 95% CI, 0.97-4.80; p=0.06) and colorectal (HR, 1.62; 95% CI, 0.92-2.87; p=0.10) cancer, and a reduced risk of prostate cancer (HR, 0.71; 95% CI, 0.43-1.17; p=0.18). In conclusion, these results do not support the hypothesis that regular use of *Ginkgo biloba* reduces the risk of cancer.

Brinkley *et al.* (2010) based the article on data from the GEM study. The GEM study included 3069 participants with a mean age of 79 years. The effects of EGb 761 on blood pressure and incident hypertension were determined. It was also examined whether the treatment effects are modified by baseline hypertension status. At baseline, 54% of the study participants were hypertensive, 28% were prehypertensive, and 17% were normotensive. Over a median follow-up of 6.1 years, there were similar changes in blood pressure and pulse pressure in the *Ginkgo biloba* and placebo groups. Although baseline hypertension status did not modify the antihypertensive effects of *Ginkgo biloba*, it did influence the changes in blood pressure variables observed during follow-up, with decreases in hypertensives, increases in normotensives and no changes in prehypertensives. Among participants who were not on antihypertensive medications at baseline, there were no differences between treatment groups in medication use over time, as the odds ratio (95% CI) for being a never-user in the *Ginkgo biloba* group was 0.75 (0.48-1.16). The rate of incident hypertension also did not differ between participants assigned to *Ginkgo biloba* vs. placebo (HR, 0.99, 95% CI, 0.84-1.15). In conclusion, the data indicate that *Ginkgo biloba* does not reduce blood pressure or the incidence of hypertension in elderly men and women.

Halil *et al.* (2005) conducted the study to assess the effects of EGb 761 on PFA-100 *in vitro* bleeding time in elderly patients with mild cognitive impairment. 40 patients aged 65-79 years received 80 mg EGb 761 three times daily for 7 days. There was no statistically significant prolongation in PFA-100 *in vitro* bleeding time or coagulation parameters in patients receiving EGb 761 after 7 days. The data about the safety of EGb 761 from the point of primary haemostasis in our elderly patient population with mild cognitive impairment casts hope for the future management of this “difficult-to-treat” population with the promising ginkgo extracts.

Naccarato *et al.* (2012): described a case report of a potential drug-herbal interaction between *Ginkgo biloba* (supplement of 300 mg daily) and Efavirenz (EFV), an antiretroviral drug, which is metabolised by CYP3A and CYP2B, in a patient that was maintained on the same regimen for 10 years. Using the Drug Interaction Probability Scale proposed by Horn *et al.* to evaluate drug interaction cases, the proposed causal relationship of virological breakthrough due to a drug interaction between *Ginkgo biloba* and EFV was calculated as probable. The authors suggested an inducing effect of *Ginkgo biloba* on EFV metabolism leading to virological breakthrough, based on the influence of *Ginkgo biloba* on the CYP450 biotransformation.

Granger (2001) describes two patients with well-controlled epilepsy, compliant with their anti-epileptic medication (1200 mg sodium valproate daily), who developed seizures within two weeks of using *Ginkgo biloba* products (not further specified, 120 mg daily). Both patients took other medications. Other medications from one patient were temazepam, aspirin and ramipril and from the other one aspirin, rivastigmine and thioridazine. After cessation of the herbal remedy, both the

patients remained seizure-free without any increase in the dosage of antiepileptic medication or change of the other medications.

Healthy participants

Keheyan *et al.* (2011) randomised 14 young healthy men in a placebo-controlled and crossover trial. Participants received EGb 761 and placebo to investigate whether a single dose of EGb 761 can improve vascular function. The arterial stiffness (DVP-SI) was slightly higher 2 hours after EGb 761 administration compared to placebo ($p<0.05$). There was no effect of either EGb 761 or placebo on pressure wave reflection (DVP-RI), peripheral augmentation index (pAIx), blood pressure and heart rate.

Köhler *et al.* (2004): This randomised, crossover trial was conducted to investigate the influence of EGb 761 on bleeding time, coagulation parameters, and platelet activity. 50 healthy male volunteers received 120 mg two times daily EGb 761 and placebo. The two treatment phases were separated by an at least 3 weeks wash-out period. The study did not reveal any evidence to substantiate a causal relationship between the administration of EGb 761 and haemorrhagic complication. As regards treatment tolerability, there were no interpretable differences between EGb 761 and placebo except for slight increase of gastrointestinal complaints during administration of the herbal extract.

Kudolo *et al.* (2004) examined the effect of EGb 761 administration on arachidonic acid (AA) metabolism in platelets. In this randomised, double-blind, placebo-controlled and crossover study 12 healthy volunteers ingested 120 mg EGb 761 or placebo daily for 3 months. After 3 months the groups switched to the other test substance for the next 3 months. In the placebo cycles, AA-stimulated thromboxane B_2 (TXB_2) production was 2581±1337 pg/10^6 platelets (range 897-5485) compared to 1668±992 pg/10^6 platelets (range 6-1668) in the EGb 761 cycles ($p<0.005$). Incubation of platelet-rich plasma with EGb 761 (150 µg/ml) completely inhibited platelet aggregation accompanied by inhibition of TXB_2 synthesis in all subjects both in the placebo (<200 pg TXB_2/10^6 platelets) and EGb 761 cycles (<120 TXB_2/10^6 platelets) ($p<0.0001$). These results support EGb 761-mediated inhibition of platelet TXB_2 synthesis *in vivo*.

Dodge *et al.* (2008): In the primary analysis the overall and event specific proportion of subjects who reported adverse events were compared between the *Ginkgo biloba* extract (GBE) and placebo groups using Fisher exact test. There was no overall difference in adverse events reported by subjects in the GBE group, compared to subjects in the placebo group (difference in proportions, $p=0.44$). However, the GBE group had more stroke or TIA incidences (7 reports, 11.7%) compared with the placebo group (0 report) ($p=0.01$, uncorrected for multiple comparisons). All strokes were non-haemorrhagic infarcts except one case; the subject with haemorrhagic infarct continues to participate in the study after the event. There were no deaths due to stroke. Four out of seven participants with stroke incidence continued to participate in the study. There was no difference in the incidence of haemorrhagic events such as gastrointestinal ulcer, epistaxis, or ecchymoses. Mortality was not different between the groups (five subjects among each group). It was concluded that the increased stroke risk will require further close scrutiny in other GBE prevention trials.

Reviews and meta-analyses:

Getov *et al.* (2007) performed the study by a literature search for safety profile assessment in clinical studies examining the effect of the standardised extract EGb 761. Safety profile of *Ginkgo biloba* products is rarely assessed in comparison with efficacy. Only five studies focus on product safety (Kanowski 1997, Le Bars 1997, Hofferberth 1994, 1989 and Schmidt 1991). Out of them, four studies state the product is well tolerated and one study, in addition, proves its safety. Safety assessment indicates the following adverse drug reactions (ADR): hypersensitivity reactions, skin reactions (erythema, edema, and itching), and gastrointestinal disorders including abdominal pain, diarrhea,

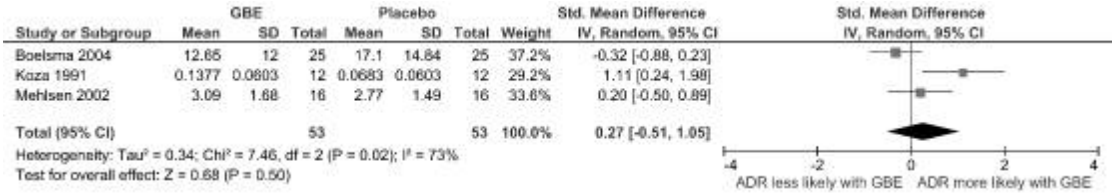
nausea and headache. From safety requirements point of view, the ADRs could be characterised as predominantly mild, with low occurrence, and presenting permissible (acceptable) risk.

IQWiG (2008): Overall, the results on adverse drug effects were inconsistent. With regard to serious adverse events and overall adverse events, there was no indication of harm caused by ginkgo. However, evidence was available that with ginkgo, more patients discontinued the study due to adverse events than with placebo.

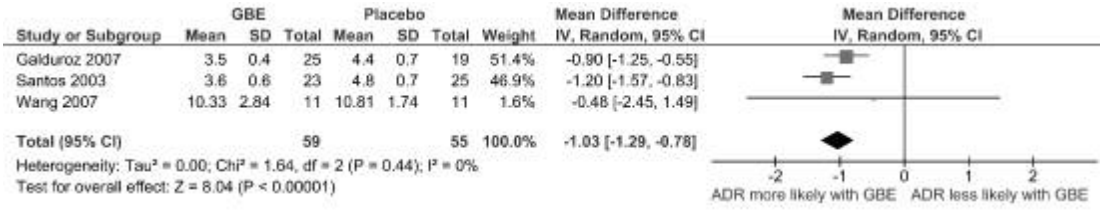
The purpose of the study by **Kellermann *et al.* (2011)** was to undertake a systematic review and meta-analysis of 18 randomised controlled trials to assess the impact of *Ginkgo biloba* leaf extract as single therapy compared with placebo on risk of bleeding, determined by assessing parameters of haemostasis.

Forest plots of meta-analysis for the outcome parameters of haemostasis

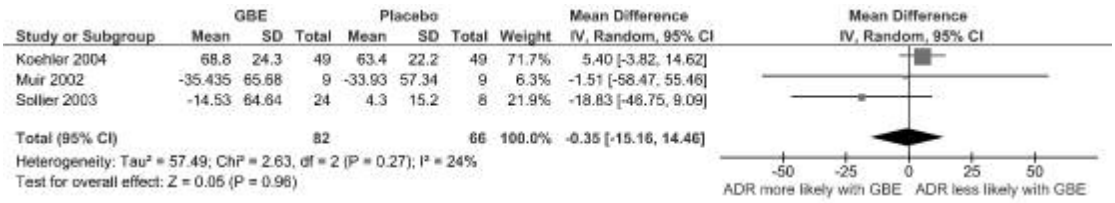
Blood flow:



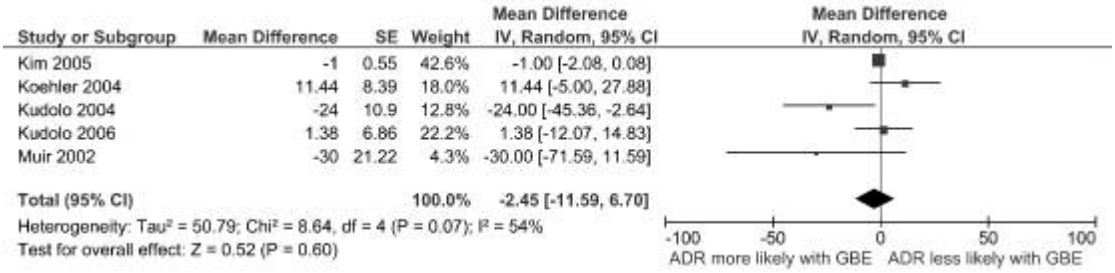
Blood viscosity:



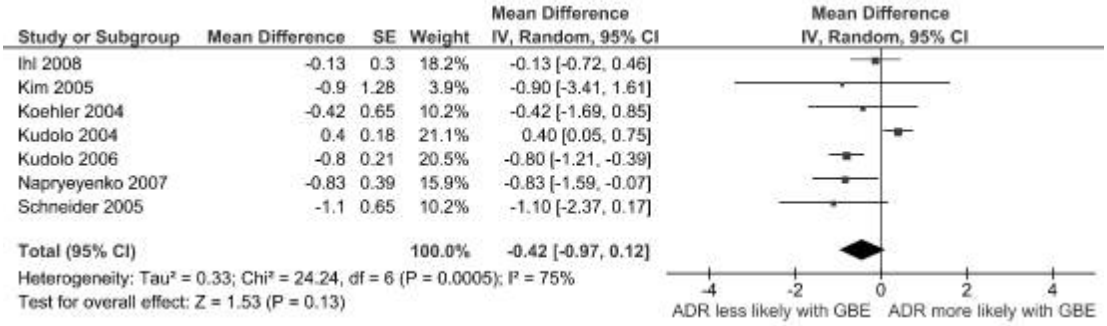
Adenosine 5´-diphosphate-induced platelet aggregation:



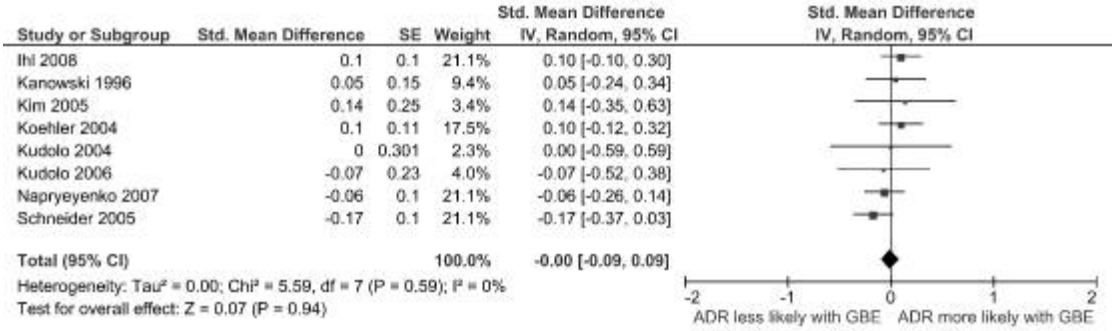
Fibrinogen concentration:



Activated partial thromboplastin time:



Prothrombin time:



Author's conclusion: Based on meta-analysis of haemostasis outcomes, comparison of mean difference or baseline change between treatment and placebo groups did not indicate a higher bleeding risk associated with standardised *Ginkgo biloba* leaf extract. This finding ultimately contributes to an informed evaluation of *Ginkgo biloba* leaf extract use, including patient self-medication.

Serious adverse events and deaths

Referring to published case reports the use of *Ginkgo biloba* has been associated with different bleeding incidents:

- Spontaneous bleeding of the nose, ecchymosis and haemorrhoidal bleeding **(Bent *et al.* 2005)**
- Postoperative bleeding **(Bebbington *et al.* 2005, Yagmur *et al.* 2005, Fessenden *et al.* 2001, Norred and Finlayson 2000)**
- Bleeding complications after liver transplantation **(Hauser *et al.* 2002)**
- Retrobulbar haemorrhage **(Fong and Kinnear 2003)**
- Hyphema **(Schneider *et al.* 2002, Rosenblatt and Mindel 1997)**
- Cerebral haemorrhage **(Meisel *et al.* 2003, Benjamin *et al.* 2001)**
- Subarachnoid haemorrhage **(Vale 1998)**
- Parietal lobe haemorrhage **(Matthews 1998)**
- Subdural haematoma **(Miller 2002, Gilbert 1997, Rowin *et al.* 1996)**

The majority of the used preparations in the above mentioned case reports were of unknown origin and quality. These were over-the-counter ginkgo products marketed in the American and UK markets. The monograph relevant preparation was only involved in two of the case reports. Since these reports

were compiled under conditions of routine medical care and not under the controlled conditions of a clinical trial, they often lacked substantial background information and, in particular, central coagulation parameters were either not available at all, or were measured under non-standardised conditions. The technical difficulties commonly associated with the standardisation of bleeding time and coagulation parameter measurement are well known.

In the absence of relevant data from controlled studies, an evaluation of case reports for evidence of a causal association between ginkgo use and bleeding includes different causality assessment elements. Besides timing of event relative to ginkgo exposure, the presence of other factors that might have caused bleeding, dechallenge and rechallenge are widely accepted elements to establish causality.

In 10 of the 13 cases providing information about duration of use exist. It was reported that ginkgo was taken for more than 6 months before the bleeding event. Two cases, one with hyphema and one with cerebral haemorrhage, had used ginkgo for 2 months. In the other case of hyphema, ginkgo was used for only 1 week.

In addition, other risk factors were reported in most cases that could have caused the bleeding event. The most common risk factor was age. In 13 of the 16 cases patients were aged 59-78. Another risk factor was coadministration of medications known to increase the risk of bleeding (aspirin, warfarin, ibuprofen or vitamin E). Other risk factors for bleeding included a fall or an operation.

Only 8 of the 16 cases specifically noted that ginkgo was stopped. None of these cases had recurrent bleeding by a follow-up time of 10 days to 4 years. Only one case reintroduced ginkgo after the bleeding event. The measured bleeding time after reintroducing ginkgo increased to >15 min (normal range 2.5 to 9.5).

Some of the authors of these case reports therefore admitted that a causal relationship between *Ginkgo biloba* and the haemorrhagic complications could not be established definitively; albeit, it could not be excluded as well. For most of the case reports a possible causal association between ginkgo and bleeding events was suggested.

According to the **pharmacovigilance database of the BfArM** 74 cases of haemorrhage during the intake of *Ginkgo biloba* medicinal products are reported in Germany (June 20, 2012). It should be keep in mind that these are suspected cases of adverse events and a causal link on an individual basis is not certainly proved. The specific location of bleeding incidences of reported adverse events (with 5 or more than 5 cases mentioned) are as followed: epistaxis, cerebral haemorrhage, gastrointestinal haemorrhage, gastric ulcer haemorrhage, haematoma, eye haemorrhage, melaena and decreased haemoglobin value. Included in the 74 reported adverse events are five cases of deaths. The deceased aged between 71 and 76 (one is unknown), where age is the most common risk factor that might have caused bleeding in these patients. Another risk factor known to increase the risk of bleeding was that four patients took at least one additional medicinal product that also has an influence on the characteristics of blood (anticoagulants in 4 out of 5 cases).

Kupiec and Raj (2005) presented a case report of a 55-year-old male who suffered a fatal breakthrough seizure, loss of consciousness and death, with no evidence of non-compliance with his anticonvulant medications. The autopsy report revealed subtherapeutic serum levels for both ingested anticonvulsants (Depakote and Dilantin). Concomitant with his prescribed medications, the decedent was also self-medicating with a cornucopia of herbal supplements and nutraceuticals a year prior to his death, prominent among which was *Ginkgo biloba*. Herbal drug interactions of *Ginkgo biloba* and CYPs metabolised drugs are known. Both anticonvulants are metabolised by CYP2C9 and CYP2C19. The proposed inducing effect of *Ginkgo biloba* on CYP2C19 activity could be a plausible explanation for the subtherapeutic levels of the two anticonvulsants, whereas these fluctuations in the concentrations could not be definitively attributed to the herb-drug interactions. However, without a qualifying lable or

a standardised quality control process, use of some nutriceutical products may prove to have hazardous consequences in individuals with a history of convulsive disorders.

5.4. Laboratory findings

Jung *et al.* (1990) conducted a randomised, placebo-controlled, single-blind, cross-over study in 10 healthy subjects to investigate the influence of 45 ml LI 1370 (dose not indicated) on blood fluidity and cutaneous microcirculation. No significant changes in blood pressure or heart rate were found in the two treatment groups. There was also no influence on haematocrit, plasma viscosity, erythrocyte rigidity, platelet and leukocyte count as well as platelet aggregation and the number of circulating platelet aggregates. In contrast, a remarkable influence on the erythrocyte aggregation was observed: a significant decrease by 15.6% ($p<0.0001$) with regard to the initial value was observed after 2 hours in the active treatment group. The blood flow in the nail fold capillaries increased significantly by about 57% ($p<0.004$) 1 hour after administration of *Ginkgo biloba* extract. In conclusion, these results indicate an improvement in blood viscosity as well as an increase in the erythrocyte flow in skin capillaries after administration of *Ginkgo biloba* extract.

5.5. Safety in special populations and situations

Dugoua *et al.* (2006): The article was prepared to systematically review the literature for evidence on the use, safety, and pharmacology of Ginkgo focusing on issues pertaining to pregnancy and lactation. There is some very weak scientific evidence from animal and *in vitro* studies that Ginkgo leaf has anti-platelet activity, which may be of concern during labour as Ginkgo use could prolong bleeding time. Low-level evidence based on expert opinion shows that Ginkgo leaf may be an emmenagogue and have hormonal properties. The safety of Ginkgo leaf during lactation is unknown. Patients and clinicians should be aware of past reports of Ginkgo products being adulterated with colchicine. The authors concluded that Ginkgo should be used with caution during pregnancy, particularly around labour where its anti-platelet properties could prolong bleeding time. During lactation the safety of Ginkgo leaf is unknown and should be avoided until high quality human studies are conducted to prove its safety.

Ang-Lee *et al.* (2001) reviewed literature from 1966 to 2000 on commonly used herbal medications in the context of the perioperative period to check if these drugs could be an endanger in surgeries. There are no randomised controlled studies on this topic. The authors recommended discontinuing the intake of *Ginkgo biloba*, particularly in the surgical population, at least 36 hours prior to surgery. The advice is based on pharmacokinetic data showing a half life of terpenoids between 3 and 10 hours. Also case reports with the perioperative concern of the potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation, led to the author's advice.

According to the **Ärzte Zeitung (09.03.2009)** acetylsalicylic acid should be discontinued 3 days prior to surgical interventions with an increased risk of bleeeding. The scientists could show that platelet function normalises faster: After 3 days already, platelets react normal in different functional tests.

5.6. Overall conclusions on clinical safety

In summary the safety analysis of the adverse event profiles of *Ginkgo biloba* and placebo were similar and there were no statistically significant differences in the rate of serious adverse events in the mentioned studies.

The following adverse events should be labeled based on information of case reports, clinical studies and of the pharmacovigilance database of the BfArM: bleeding of individual organs (eye, nose, cerebral

and gastrointestinal haemorrhage), headache, dizziness, mild gastrointestinal complaints (such as diarrhoea, abdominal pain, nausea and vomiting), hypersensitivity reactions (allergic shock) and allergic skin reactions (erythema, oedema, itching and rash).

The following adverse events were additionally reported in clinical studies: angina pectoris, hypertension, respiratory tract infection and tinnitus. The observation of the adverse event angina pectoris is contradictory to the above mentioned clinical studies of Kuller *et al.* (2010) and DeKosky *et al.* (2008). Both studies analysed the secondary results of the GEM study and stated that there were no differences in incident myocardial infarction (n=164), angina pectoris (n=207), or stroke (151) between *Ginkgo biloba* and placebo. Regarding hypertension the study by Brinkley *et al.* (2010) determined the effects of EGb 761 on incident hypertension. It was shown that the rate of incident hypertension did not differ between participants assigned to *Ginkgo biloba* vs. placebo.

Efavirenz, being a substrate, an inhibitor and an inducer of CYPs, exhibits multiple interactions with the P450 system. Evaluation of drug interactions with efavirenz is further complicated because efavirenz is reported to enhance its own metabolism during repeated administration. Thus the exact underlying mechanism remains unresolved. *Ginkgo biloba* preparations may lower EFV plasma levels by the induction of CYP3A4, an EFV metabolising enzyme. In conclusion an intake of *Ginkgo biloba* containing medicinal products can decrease human plasma EFV levels, may result in virological failure and should be discouraged.

It is recommended to avoid the use of *Ginkgo biloba* containing products in epileptic patients and those on medications known to lower seizure threshold. The risk of onset of further seizures is addressed in the special warning section.

Laboratory findings support the effect of *Ginkgo biloba* on blood flow and therefore advice for patients with a pathologically increased bleeding tendency and concomitant anticoagulant and antiplatelet treatment is included in the special warning section.

Usually, pregnant women are not in an age with major relevance of dementia. However isolated cases of dementia disease in younger patients may not be excluded. *Ginkgo biloba* extracts may impair the ability of platelets to aggregate, which may be of concern during labour because ginkgo use could prolong bleeding time thereby increasing the disposition for bleeding. Therefore, use in pregnancy is contraindicated.

Concerning lactation, it is unknown whether *Ginkgo biloba*/metabolites are excreted in human milk. A risk to the newborns cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue from *Ginkgo biloba* containing medicinal product therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

In consideration of a similar mode of action of *Ginkgo biloba* and acetyl salicylic acid, preparations containing Ginkgo should be discontinued as a precaution 3 to 4 days prior to surgery.

6. Overall conclusions

A specified preparation of *Ginkgo biloba* fulfils the requirements of well-established use. There are different clinical studies which demonstrate benefits of *Ginkgo biloba* in patients with mild dementia especially above the age of 50 years, which are displayed in the indication: “Herbal medicinal product for the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia. The results are supported by meta-analysis of several clinical trials. Overall, there is a reasonable safety profile of *Ginkgo biloba* preparations. With respect to side effects bleeding events have been observed. This signal can be adequately addressed by appropriate labelling. Existing data on interactions are as well adequately addressed in the respective section. The evaluation of the NTP

technical report, which was addressing toxicological concerns, led to the conclusion that at present there is no proof for an increased cancer risk identified for patients taking Ginkgo folium medicinal products at their approved posology. Overall the benefit-risk-ratio is considered positive.

Criteria for a traditional use are fulfilled for a powder usually administered in a capsule. The discussion finally concluded that the following indication reflects the traditional use and complies with the requirements of traditional herbal medicinal products: “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”. All safety relevant labelling for traditional use are based on data reported for extracts of *Ginkgo biloba* on the well-established use part of the monograph. It cannot be excluded that they may occur with the powder. A Community list entry was not established due to lack of specific data on genotoxicity. Moreover, it is questionable, if the safety profile of Ginkgo in general is suitable to establish a Community list entry.

Annex

List of references