Drugs & Therapy Perspectives (2018) 34:358–366
https://doi.org/10.1007/s40267-018-0537-8

ADIS DRUG Q&A

Ginkgo biloba extract EGb 761® in the symptomatic treatment of mild-to-moderate dementia: a profile of its use

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Published online: 11 July 2018
© Springer Nature 2018, corrected publication 2018

Abstract
EGb 761® (Tanakan®) is a standardized extract of *Ginkgo biloba* leaves that has demonstrated protective properties against neuronal and vascular damage. Overall, in randomized, placebo-controlled clinical trials and meta-analyses in adults with mild-to-moderate dementia, EGb 761® displayed positive effects, with changes from baseline in outcomes related to cognition, behaviour and global change that are generally better than those shown with placebo. EGb 761® is generally well tolerated, with no safety issues being identified during its many years of widespread use.

Adis evaluation of *Ginkgo biloba* extract EGb761® in the symptomatic treatment of mild to moderate dementia

Standardized pharmaceutical-quality extract
Has a range of neuroprotective effects, including acting as a potent antioxidant and scavenger of free radicals
Has a positive impact on the symptoms, including cognitive impairment, of mild-to-moderate dementia in adults
Generally well tolerated, with no safety issues

What is the rationale for using EGb 761® in mild-to-moderate dementia?

Dementia is a chronic or progressive condition that is characterized by impaired cognitive capacity and dependency on others, the severity of which is greater than that considered a consequence of normal aging [1]. Common forms of dementia include Alzheimer's disease (AD) and vascular dementia (VD), which affect many aspects of neurological function, including memory, thinking, orientation, comprehension, learning ability and judgement. The molecular pathogenesis of dementia of the AD type is complex and likely to involve several factors [1]. The most important of these are thought to be the effects of oxidative stress, abnormal formation and aggregation of the β-amyloid protein (Aβ), hyperphosphorylation of the tau protein, and changes in the cholinergic system involving glutamatergic neurotransmission alterations [1, 2].

Treatment options for patients with dementia are limited [3]. Acetylcholinesterase inhibitors (AChEIs) may improve cognitive function in some patients with mild-to-moderate dementia, but current drug therapies cannot cure or prevent its progression [1, 3]. In recent years, the interest in developing natural plant-derived compounds for the treatment of cognitive decline has increased [4]. The *Ginkgo biloba* tree is the source of one such agent, with extracts from the leaves having been widely used for their health promoting properties for many decades [4, 5]. EGb 761® (Tanakan®) is a standardized extract of *Ginkgo biloba* leaves that has demonstrated protective properties against neuronal and vascular damage [4, 5]. Other *Ginkgo biloba* extracts (many as herbal dietary supplements) have been marketed over the years. [6, 7]. As these extracts are not standardized to the specifications used in the formulation of EGb 761®, they are not considered pharmaceutically equivalent to EGb 761® [6, 7].

For whom is EGb 761® indicated?

EGb 761® is approved throughout Europe for the symptomatic treatment of adults with cognitive impairment and mild-to-moderate dementia [8, 9]. Table 1 summarizes

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the use of EGb 761® in this indication in Europe [based on the Czech [8] and Lithuanian [9] summaries of product characteristics (SPCs)]. The use of EGb 761® to treat other conditions is beyond the scope of this review. Consult local information for further details.

How does EGb 761® work?

EGb 761® has numerous pharmacological actions that derive from the various constituents of the herbal extract, acting separately or synergistically [5, 10–12]. The most pharmacologically important constituents in the treatment of cognitive decline are the flavonoid glycosides and terpene trilactones [5, 10].

Neuroprotective effect

Various mechanisms are associated with the neuroprotective effect of EGb 761®, including free radical-scavenging, antioxidant effects, improvement in mitochondrial function, regulation of neurotransmitters, and effects on neuronal plasticity (Table 2) [5, 10, 11]. In addition, preliminary results with EGb 761® in adults with memory impairment suggest mild enhancement of prefrontal dopamine [13].

EGb761® improved learning and memory and had a beneficial effect on age-related behaviour in animals, as well as being associated with improvements in memory in healthy volunteers (Table 2).

Effects on lesions associated with Alzheimer's disease

EGb 761® was associated with protective activity against Aβ-induced neurotoxicity [14]. Aβ is involved in the pathogenesis of AD and is the main constituent of amyloid plaques found in the brains of AD patients [2, 15]. In addition, studies indicate that EGb 761® induces amyloid precursor protein metabolism toward α-secretase pathway, preventing the formation of Aβ peptides [16].

Table 1 Review of the summary of product characteristics of oral EGb 761® (Tanakan®) in mild-to-moderate dementia in Europe (based on the Czech [8] and Lithuanian [9] summaries of product characteristics)

How is EGb 761® available?	
Coated tablets containing 40 mg/tablet or oral solution containing 40 mg/mL of a standardized dry extract of *Ginkgo biloba* (EGb 761®), including 24% ginkgoflavone glucosides and 6% terpene tri lactones (A and B ginkgolides and bilobalide)	
How should EGb 761® be administered and stored?	
Usual dosage	120–240 mg/day (i.e. 3–6 EGb 761® 40-mg tablets or 3–6 mL of EGb 761® 40 mg/mL solution) divided into 2 or 3 doses; take with meals
Preparation and administration	Tablets: take with half a glass of water
	Oral solution: measure solution using the dispenser provided; mix with half a glass of water, then drink; place dispenser in the special tray after each use
Storage	At room temperature in a dark place
What are the contraindications to the use of EGb 761®?	
Hypersensitivity to standardized *Ginkgo biloba* extract (EGb 761®) or any of the other ingredients [i.e. lactose, cellulose, corn starch, colloidal silicon dioxide, talc, magnesium stearate in the tablets; soluble essential oils of orange and lemon, saccharin sodium, ethanol (450 mg/mL) in the oral solution]	
How should EGb 761® be used in special populations?	
Pregnant and breast-feeding women	Should not be used (lack of clinical data)
Patients with congenital galactosemia, lactase deficiency or glucose-galactose malabsorption	Tablet formulation should not be used (formulation contains lactose)
What is the pharmacokinetic profile of orally administered EGb 761®?	
Bioavailability	80–90% (A and B ginkgolides and bilobalide)
Time to peak plasma concentration	1–2 h
Plasma half-life	4 h (A ginkgolide and bilobalide) to 10 h (B ginkgolide)
Elimination	Does not undergo metabolism in the body; primarily excreted in the urine
What clinically relevant drug interactions may potentially occur with EGb 761®?	
Drugs mainly metabolized by cytochrome P450 (CYP) 3A4 with a narrow therapeutic index	Use concomitantly with caution; in clinical interaction studies, EGb 761® either induced or inhibited cytochrome P450 isoenzymes (e.g. concomitant administration of EGb 761® and midazolam affected midazolam concentrations, suggesting some interaction via CYP3A4)
Drugs that provoke a disulfiram-alcohol-like reaction and CNS depressants	Take into account the presence of ethanol (450 mg/mL) in the solution formulation of EGb 761® when using such medications

Table 2 A summary of selected EGb 761® neuroprotective mechanisms of action and potential therapeutic effects

Mechanisms of neuroprotective effect in vitro and in animal studies
Demonstrated potent antioxidant and scavenging activities against various reactive oxygen species (including superoxide, peroxyl and hydroxyl radicals), enhanced the activities of superoxide dismutase and catalase, and decreased lipid peroxidation in the striatum, substantia nigra and hippocampus of rats [18]
Had protective effects against apoptosis induced by oxidative stress in cultures of rat cerebellum [19]
Protected against age-related mitochondrial DNA impairment and glutathione oxidation in rats by preventing high levels of peroxide generation and did not affect enzyme activities of the mitochondrial respiratory chain [20]
Led to a significant recovery of spatial memory, protected the hippocampal CA1 neurons and inhibited the decrease in plasma superoxide dismutase activity in a model of vascular dementia in gerbils [21]
Improved spatial learning and memory, and had beneficial effects on synaptic efficacy and plasticity in the hippocampus CA1 area in aged rodents [22, 23]
Increased cell proliferation in the hippocampus of young and old mice, and increased the total number of neuronal precursor cells in a dose-dependent manner [24]
Protected against ischaemia- and glutamate-induced neuronal death via anti-excitotoxicity, inhibition of free radical generation, scavenging of reactive oxygen species and regulation of mitochondrial gene expression [25, 26]
Modified the activity of target genes and transcription factors, including those implicated in the stress response [27]
Alleviated oxidative stress and some neurotransmitter adverse effects induced by aluminium chloride [28]
Effects on lesions or lesion precursors of AD
Dose-dependently protected against Aβ-induced neurotoxicity [14, 29, 30]
Dose-dependently attenuated memory impairment and cell apoptosis in galactose-induced dementia [31]
Dose-dependently inhibited the formation of Aβ-derived diffusible neurotoxic ligands, attenuated mitochondrial-initiated apoptosis and decreased caspase-3 activity [32]
Directly inhibited Aβ aggregation and decreased caspase 3 activity [33]
Blocked an age-dependent decline in spatial cognition without altering Aβ levels and without suppressing protein oxidation [34]
Dose-dependently increased αAPP release via a protein kinase C-independent manner, thereby demonstrating ability to directly inhibit amyloid fibril formation [16]
Lowered circulating free cholesterol and inhibited the production of APP and Aβ-peptide [35]
Decreased Aβ fibril formation [36]
Improved oxygen consumption in mitochondria from APP cells and led to an up-regulation of mitochondrial DNA [37]
May modulate the phosphorylation of tau protein, implicated in the pathogenesis of AD [38]
Neurological effects in animal studies
Reduced the extent of hippocampal CA1 cell loss ($p < 0.01$–0.001); effect was sustained for ≥ 40 days after ischaemia [39]
Demonstrated a positive effect on learning and memory ability [40]
Improved cognitive performance and extended longevity in aged rats [41]
Promoted spatial learning [42]
Reduced impairment of learning and memory abilities and other harmful effects induced by high, sustained positive acceleration [43]
Improved plasticity mechanisms involved in vestibular compensation promoting balance recovery [44]
Neurological effects in humans
Improved behavioural performance ($p < 0.05$) and increased brain steady-state visually evoked potential amplitude and latency after 2 weeks' treatment in an object working memory task in a randomized crossover study in healthy males [45]
Mildly enhanced prefrontal dopamine in a randomized 8-week trial in elderly volunteers with subjective memory impairment [13]

Aβ amyloid β, *AD* Alzheimer's disease, *APP* amyloid precursor protein

In vitro and in vivo studies indicate that EGb 761® protects against Aβ-induced neurotoxicity by blocking the pathological cascade of Aβ-induced events, including reactive oxygen species generation and mitochondrial dysfunction, as well as dose-dependently protecting against Aβ-induced apoptosis and neurotoxicity (Table 2) [10].

What is the pharmacokinetic profile of EGb 761®?

After oral administration of EGb 761® in humans, the flavonoid glycosides and terpene trilactones reach the CNS in measurable concentrations [17]. The terpene trilactones, including A and B ginkgolide and bilobalide, reach

maximum plasma concentrations within 1–2 h and are characterized by relatively short half-lives (Table 1). By 24 h after administration, terpene trilactones cannot be detected in the brain [17]. The half-life of the flavonoids contained in EGb 761® is about 10–17 h [17]. Because of the relatively short half-lives of the active constituents, EGb 761® should be taken more than once daily (Table 1) [8, 9, 17].

What is the efficacy of EGb 761® in mild-to-moderate dementia?

Compared with placebo

Numerous studies have evaluated *Ginkgo biloba* extracts in the treatment of AD and/or VD. This section focuses on the primary/co-primary endpoint-related results in the intent-to-treat (ITT) populations of randomized, controlled trials (RCTs) of EGb 761® 120–240 mg/day in divided doses (as per the recommended regimen) versus placebo in the symptomatic treatment of mild-to-moderate AD and/or VD [46–58], and meta-analyses [59–63] of these [46–51, 53–58] and other RCTs [64, 65]. Only the key results of fully-published RCTs in a total of > 100 patients [46–51, 53–58] and recent meta-analyses (i.e. published in 2013 or onwards) [59–63] are discussed. The diagnostic criteria for dementia varied between RCTs, which may have affected trial outcomes.

In the total populations, where reported, the proportion of patients who discontinued treatment before the end of the 22–26 week trials was generally comparable between the EGb 761® 120–240 mg/day and placebo groups (2–28 vs 2–23%) [46, 47, 50, 51, 53, 55, 57].

Cognition

In RCTs with primary cognition-related endpoints, EGb 761® was significantly more effective than placebo in improving cognition as measured by changes from baseline in Syndrom-Kurz test (SKT; a psychometric test that assesses memory and attention) scores in most [47, 53, 56], but not all [51, 58] of the RCTs that assessed this outcome (Table 3). In subgroup analyses of these RCTs in patients with AD [47, 55, 57] and/or VD [55, 57], changes from baseline in SKT scores also significantly favoured EGb 761® over placebo (Table 3). Likewise, cognition, as assessed by changes from baseline in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores, decreased to a significantly lesser extent with EGb 761® than with placebo at 52 weeks in one RCT (Table 3) [49].

There were no significant treatment differences (TDs) in ADAS-cog scores in the overall population of two other RCTs [46, 50] that assessed this outcome. However, in the subgroup of patients with NPS in one of these RCTs [46], changes from baseline in ADAS-cog scores significantly favoured EGb 761® 240 mg/day over placebo (Table 3). Likewise, although there was no significant difference between EGb 761® 120 or 240 mg/day and placebo with regard to the proportion of patients with AD who showed an improvement or no change in their condition as assessed by the Alzheimer's Disease Cooperative Society Clinical Global Impression of Change scale (ADCS-CGI) [46], ADCS-CGI scores significantly favoured EGb 761® 120 mg/day over placebo in the NPS subgroup (Table 3) [46]. The other RCT that showed no significant TDs in ADAS-cog scores [50] has been criticized for being under powered [66]. In the two RCTs that assessed the global change in cognition using the Clinical Global Impression (item 2) [CGI-2] scale, EGb 761® 160–240 mg/day was significantly more effective than placebo [47, 51].

In the ITT population in one RCT [47], the proportion of patients who responded to treatment (defined as a decrease from baseline in ADAS-cog scores of ≥ 2 or 4 points) was determined by estimating ADAS-cog scores based on measured SKT scores. Significantly more EGb 761® 240 mg/day recipients than placebo recipients were ≥ 2-point responders (61 vs 37%; $p < 0.001$) and ≥ 4-point responders (35 vs 19%; $p = 0.01$) in the overall population. Corresponding results in the subgroup of patients with AD were comparable (66 vs 34%; $p < 0.001$) and (35 vs 19%; $p = 0.02$) [47].

EGb 761® 240 mg/day was significantly ($p < 0.01$) more effective than placebo with regard to mean changes from baseline/screening in secondary cognition-related outcomes in the overall populations and the subgroups of patients with AD and/or VD in some trials [i.e. Verbal Fluency Test (VFT) [53–57], Test for Early Detection of Dementia with Discrimination from Depression (TE4D) cognitive score [53] and Clock Drawing Test (CDT) [56, 57]]. However, there were no significant differences between EGb 761® 160/240 mg/day and placebo with regard to changes from baseline in test scores used to assess trail-making speed, digit memory span and verbal learning [52].

Activities of daily living

In the 52-week trial [48], the ability to perform activities of daily living (ADL), as assessed by changes from baseline in Geriatric Evaluation by Relative's Rating Instrument (GERRI) scores, improved to a significantly greater extent with EGb 761® 120 mg/day than with placebo. However, there were no significant differences between EGb 761® (160/240 [51] or 240 mg/day [47]) and placebo in other RCTs that assessed changes from baseline in ADL using

Table 3 Efficacy of EGb 761® 120–240 mg/day (in divided doses) in the treatment of mild-to-moderate Alzheimer's disease or vascular dementia as evaluated by primary/co-primary endpoints in randomized placebo-controlled trials with > 100 patients and a duration of 22–52 weeks

Study (duration in weeks)	EGb 761® [mg/day] (no. of pts) vs PL (no. of pts)	Mean change from baseline in score in the ITT population at study end (unless otherwise indicated)
Pts with AD		
Schneider et al. [46] (26)	All pts: EGb 761® 120 (169) or 240 (170) vs PL (174)	ADAS-cog: 1.6 and 1.3 vs 0.9
		ADCS-CGIC: 61 and 62 vs 55% of pts improved/had no change
	NPS subgroup: EGb 761® 120 (51) or 240 (42) vs PL (47)	ADAS-cog: 0.8 and 0.6* vs 2.8
		ADCS-CGIC: 60* and 60 vs 39% of pts improved/had no change
Pts with AD or VD		
Kanowski et al. [47] (24)	All pts: EGb 761® 240 (106) vs PL (99)	SKT: −2.1** vs −1.0 (TD −1.1; 95% CI −2.0 to −0.2)
		NAB: −0.8 vs −0.4 (TD −0.4; 95% CI −1.0 to −0.1)
		CGI-2: 4.1** vs 4.5 (TD −0.4; 95% CI −0.78 to −0.1)
	AD subgroup: EGb 761® 240 (79) vs PL (79)	SKT: −2.3** vs −1.0 (TD −1.3; 95% CI −2.3 to −0.3)
		NAB: −1.0 vs −0.4 (TD −0.6; 95% CI −1.3 to −0.1)
		CGI-2: 4.1** vs 4.6 (TD −0.5; 95% CI −0.8 to −0.2)
Le Bars et al. [48, 49] (52)	EGb 761® 120 (155) vs PL (154)	ADAS-cog: 0.1* vs 1.5 (TD −1.4; 95% CI −2.7 to −0.0)
		GERRI: −0.06** vs 0.08 (TD −0.14; 95% CI −0.23 to −0.04)
		CGIC: 4.2 vs 4.2 (TD 0.0; 95% CI −0.1 to 0.2)
	AD subgroup: EGb 761® 120 (120) vs PL (116)	ADAS-cog: −0.2* vs 1.5 (TD −1.7; 95% CI −3.2 to −0.2)
		GERRI: −0.09*** vs 0.09 (TD −0.19; 95% CI −0.28 to −0.08)
		CGIC: 4.2 vs 4.2 (TD 0.0; 95% CI −0.2 to 0.2)
McCarney et al. [50] (24)	EGb 761® 120 (88) vs PL (88)	ADAS-cog: (aTD −0.823; 95% CI −2.701 to 1.055)
		PR-QOL-AD: (aTD −0.187; 95% CI −1.542 to 1.168)
van Dongen et al. [51, 52] (24)	EGb 761® 160/240 (79) vs PL (44)	SKT: −0.8 vs −1.2 (0.4; 90% CI 0.0 to 1.7)
		NAA: −1.4 vs −1.4 (0.0; 90% CI −1.6 to 1.6)
		CGI-2: 1.2 vs 1.1 (0.0; 90% CI −0.3 to 0.4)
Pts with AD or VD with NPS		
Herrschaft et al. [53] (24)	EGb 761® 240 (200) vs PL (202)	SKT: −2.2*** vs −0.3
		NPI: −4.6*** vs −2.1
Ihl et al. [54, 55] (24)	All pts: EGb 761® 240 (202) vs PL (202)	SKT: −1.4*** vs 0.3
		NPI: −3.2*** vs 0.0
	AD subgroup: EGb 761® 240 (163) vs PL (170)	SKT: −1.4*** vs 0.3
		NPI: −2.9*** vs 0.2
	VD subgroup: EGb 761® 240 (39) vs PL (32)	SKT: −1.4* vs 0.0
		NPI: −4.5* vs −1.3
Napryenyenko et al. [56, 57] (22)	All pts: EGb 761® 240 (198) vs PL (197)	SKT: −3.2*** vs 1.3 (TD 4.5; 95% CI 4.1 to 5.0)
	AD subgroup: EGb 761® 240 (104) vs PL (110)	SKT: −3.0** vs 1.2
	VD subgroup: EGb 761® 240 (94) vs PL (87)	SKT: −3.4** vs 1.5
Nikolova et al. [58] (22)	EGb 761® 240 (203) vs PL (205)	SKT: −2.2 vs −2.0
		NPI: −3.8 vs −3.1

AD Alzheimer's disease, *ADAS-cog* AD Assessment Scale-cognitive subscale, *ADCS-CGIC* AD Cooperative Study-Clinical Global Impression of Change, *aTD* adjusted TD, *CGI-2* Clinical Global Impression (item 2), *GERRI* Geriatric Evaluation by Relative's Rating Instrument, *ITT* intent-to-treat, *NAA* Nürnberger-Alters-Alltagsaktivitäten-Skala, *NAB* Nürnberger-Alters-Beobachtungs-Skala, *NPI* Neuropsychiatric Inventory, *NPS* neuropsychiatric symptoms, *PL* placebo, *pts* patients, *PR-QOL-AD* participant-rated quality of life in AD, *SKT* Syndrom-Kurz test, *TD* treatment difference, *VD* vascular dementia

*$p < 0.05$, **$p \leq 0.01$; *** $p < 0.001$ vs PL

the Nürnberger-Alters-Beobachtungs-Skala (NAB) [47] or Nürnberger-Alters-Alltagsaktivitäten-Skala (NAA) [51] as a co-primary endpoint (Table 3).

In the overall populations and the subgroups of patients with AD or VD, EGb 761® 240 mg/day was significantly ($p < 0.01$) more effective than placebo with regard to the

secondary endpoints of changes from baseline in AD-ADL International scale (ADL-IS) [53–55] and Gottfries-Bråne-Steen (GBS)-ADL scores [56, 57] in some trials. EGb 761® 160/240 mg/day was more effective than placebo with regard to changes from baseline in self-perceived ADL, but not when data were corrected for confounding [52].

Behaviour and other outcomes

As assessed by Neuropsychiatric Inventory (NPI) scores as a primary endpoint in RCTs in patients with neuropsychiatric symptoms (NPS), EGb 761® 240 mg/day was significantly more effective in improving behaviour than placebo in all [53–55] but one [58] RCT that assessed this outcome (Table 3).

With regard to secondary outcomes, EGb 761® 240 mg/day was significantly ($p < 0.05$) more effective than placebo with regard to the mean change from baseline in behaviour-related outcomes (NPI [56, 57] and NPI caregiver distress score [53–57]) in patients with dementia [56] (including the subgroups of patients with AD or VD [57]) and patients with dementia with NPS [53, 54] (including the subgroups of patients with AD or VD [55]) in the RCTs that evaluated these outcomes. There were no significant differences between EGb 761® 160/240 mg/day and placebo with regard to changes from baseline in geriatric symptom, depressive mood, and self-perceived health and memory status scores [52].

Changes from baseline in health-related quality-of-life (HR-QOL), as assessed by participant-rated Quality of Life in AD scores, did not differ to a statistically significant extent between EGb 761® 120 mg/day and placebo in the single RCT in which this was a co-primary endpoint (Table 3) [50]. In the overall populations and the subgroups of patients with AD or VD in some trials, EGb 761® 240 mg/day was significantly ($p < 0.03$) more effective than placebo with regard to the mean change from baseline in secondary global change outcomes (ADCS-CGIC [53–55]) and HR-QOL (DEMQOL-Proxy total score in the total [53–55] and AD (but not VD) populations [55]) and GBS overall geriatric assessment scale [56, 57].

Meta-analyses

Meta-analyses (which included most of the RCTs in Table 3 and/or other RCTs) have generally shown that EGb 761® provides benefits in the symptomatic treatment of dementia (Table 4) [59–63]. The inclusion criteria for each meta-analysis differed; however, regardless of which RCTs were included, EGb 761® 120–240 mg/day was generally associated with improvements from baseline in cognition [59–63] and the ability to perform ADL [60, 62, 63], as well as improvements in global ratings [60, 63]. Of note, where reported, most of these meta-analyses had a high degree of heterogeneity, as shown by I^2 scores of 81–100% and $p < 0.00001$ for heterogeneity for all analyses [60–63], with the exception of one ADL analysis with a moderately high I^2 score of 62% [62]; therefore, the results should be interpreted with caution.

Compared with acetylcholinesterase inhibitors (AChEIs)

AChEIs, such as donepezil, galantamine and rivastigmine, are indicated for the symptomatic treatment of dementia in patients with mild-to-moderate dementia. Three RCTs have compared the efficacy of EGb 761® monotherapy [65, 67], EGb 761® + an AChEI [67, 68] and AChEI monotherapy [65, 67, 68].

The efficacy of EGb 761® 160 mg/day was not significantly different to that of donepezil 5 mg/day in the ITT population of a small ($n = 76$) 24-week RCT [65]. Cognition (as assessed by changes from baseline in SKT and CGI scores) significantly ($p = 0.01$) improved in the EGb 761® and donepezil groups relative to the placebo group. Cognition, as measured by Mini-Mental State Examination (MMSE) scores, improved in the EGb 761® and donepezil groups, and declined slightly in the placebo group, but the TDs were not statistically significant [65].

In 828 patients in the ICTUS (Impact of Cholinergic Treatment Use) study [68], the addition of EGb 761® (120 mg/day in 56% of patients) to treatment with an AChEIs (i.e. donepezil, galantamine, rivastigmine) provided some additional cognitive benefits relative to AChEI monotherapy. At 12 months, the TD for the change from baseline in MMSE scores favoured EGb 761® + an AChEI over AChEI monotherapy [1.86 ± standard error (SE) of 0.67; $p = 0.006$]. At 6 months, however, the TD for the change from baseline in MMSE scores (0.92 ± SE 0.55) did not reach statistical significance. There were also no statistically significant TDs with regard to the changes from baseline in ADAS-Cog and Instrumental-ADL scale scores at 6 and 12 months [68].

Likewise, in a small 22-week RCT in 96 patients with AD with NPS, changes from baseline in all outcome measures (SKT, NPI, GBS-ADL subscale, Hamilton Rating Scale for Depression, CDT and VFT) and response rates showed an apparent tendency to favour combination treatment with EGb 761® 240 mg/day + donepezil 5/10 mg/day over monotherapy with EGb 761® 240 mg/day or donepezil 5/10 mg/day [67]. However, the results did not differ to a statistically significant extent [67].

What is the tolerability profile of EGb 761®?

EGb 761® is generally well tolerated, according to the results of an in-depth analysis that combined toxicological data, long-term safety data from clinical studies and literature reports [70]. In addition, meta-analyses [60, 61, 63]

Table 4 Efficacy of EGb 761® 120–240 mg/day (in divided doses) vs placebo in the treatment of mild-to-moderate Alzheimer's disease or vascular dementia as evaluated by selected systematic reviews an meta-analyses of randomized, controlled trials

Meta-analysis	No. of RCTs analyzed for outcome(s)	No. of pts (EGb 761® 120–240 mg/day vs PL)	Results for key outcomes (95% CI)
Brondino et al. [59]	7 [46, 48, 51, 54, 56, 64, 69]	897 vs 855	Cognition score: SMD −0.56* (−1.026 to −0.095)
	6 [46, 48, 51, 54, 56, 69]	892 vs 844	ADL score: SMD −0.58 (−1.131 to −0.029)
Gauthier and Schlaefke [60]	7 [46–48, 53, 55, 56, 58]	1207 vs 1208	ADAS-cog score: SMD −0.52* (−0.98 to −0.05)
		1210 vs 1206	ADL score: SMD −0.44*** (−0.68 to −0.19)
		1223 vs 1215	ADCS-CGIC score: SMD −0.52*** (−0.92 to −0.12)
Hashiguchi et al. [61]	7 [47, 51, 53, 54, 56, 64, 65]	819 vs 779	SKT score: SMD −0.9** (−1.46 to −0.34)
Jiang et al. [62]	6 [46, 47, 49, 51, 53, 54]	1062 vs 855	Cognition score: SMD −0.28* (−0.51 to −0.05)
		1064 vs 1296	ADL score: SMD −0.22** (−0.37 to −0.06)
Tan et al. [63]	6 [46, 47, 51, 53, 54, 56]	1285 vs 1296	ADAS-cog score : SMD −2.86*** (−3.18 to −2.54)
		1262 vs 1268	ADL score: SMD −0.36*** (−0.44 to −0.28)
	5 [46, 47, 51, 53, 54]	1001 vs 1006	OR of improved ADCS-CGIC: 1.88*** (1.54 to 2.29)

AD Alzheimer's disease, *ADAS-cog* AD Assessment Scale-cognitive subscale, *ADCS-CGIC* AD Cooperative Study-Clinical Global Impression of Change, *ADL* activities of daily living, *OR* odds ratio, *PL* placebo, *pts* patients, *SKT* Syndrom-Kurz test, *SMD* standardized mean difference from baseline; treatment difference

*$p < 0.05$, **$p \leq 0.01$; ***$p < 0.001$ vs PL

of the tolerability of EGb 761® in RCTs, and the European Medicines Agency assessment report on *Ginkgo biloba* [71], did not find any safety issues. European SPCs for EGb 761® states that gastrointestinal upset, skin reactions and headache occur rarely during treatment [8, 9].

In response to reports of spontaneous bleeding in patients treated with *Ginkgo biloba*, two randomized, double-blind, placebo-controlled studies evaluated bleeding-related endpoints [72, 73]. In healthy volunteers, *Ginkgo biloba* extract (120, 240 and 480 mg/day for 14 days) did not cause any changes in platelet function or coagulation [72]. Similarly, in elderly patients with peripheral artery disease or at risk of cardiovascular disease, EGb 761® 300 mg/day coadministered with aspirin 325 mg/day for 4 weeks did not have any clinically or statistically significant effect on coagulation parameters [73].

What is the place of EGb 761® in the symptomatic treatment of mild-to-moderate dementia?

EGb 761® has positive effects on the symptoms of mild-to-moderate dementia, with changes from baseline in outcomes related to cognition, behaviour and global change that are generally better than those shown with placebo. The efficacy of EGb 761® in the treatment of mild-to-moderate dementia may be more marked in patients with NPS. The mechanisms of its neuroprotective effect are thought to be largely attributable to its antioxidant activity and ability to scavenge free radicals, and to its protective activity against Aβ-induced neurotoxicity and synthesis. The herbal extract is generally well tolerated, with no safety issues having been identified during many years of widespread use.

Limited data suggest that the efficacy of EGb 761® may be comparable to that with donepezil in patients with mild-to-moderate AD-related dementia, and that additional benefits may be gained by adding EGb 761® to existing treatment with an AChEI. Further studies on the efficacy of EGb 761® alone or in combination with an AChEI versus AChEI monotherapy, as well as long-term studies, would help confirm its place in the treatment of mild-to-moderate dementia.

Acknowledgements The manuscript was reviewed by: *M. Mazza*, Department of Neurosciences, Institute of Psychiatry, Catholic University of Sacred Heart, Rome, Italy; *M.C. Woodward*, Aged and Residential Care Services, Austin Health, University of Melbourne, Heidelberg, VIC, Australia; *W.S. Zirker*, Division of Geriatric Medicine, Crozer-Chester Medical Center, Upland, PA, USA. During the peer review process, Ipsen Pharma, the marketing-authorization holder of EGb 761®, was also offered an opportunity to provide a scientific accuracy review of their data. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with ethical standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest K. McKeage and K.A. Lyseng-Williamson are employees of Adis/Springer, are responsible for the article content and declare no conflicts of interest.

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