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Health Technology Assessment (HTA)

**HTA Protocol**

# Ginkgo biloba in patients with decreasing mental performance, peripheral arterial occlusive disease, vertigo, or tinnitus

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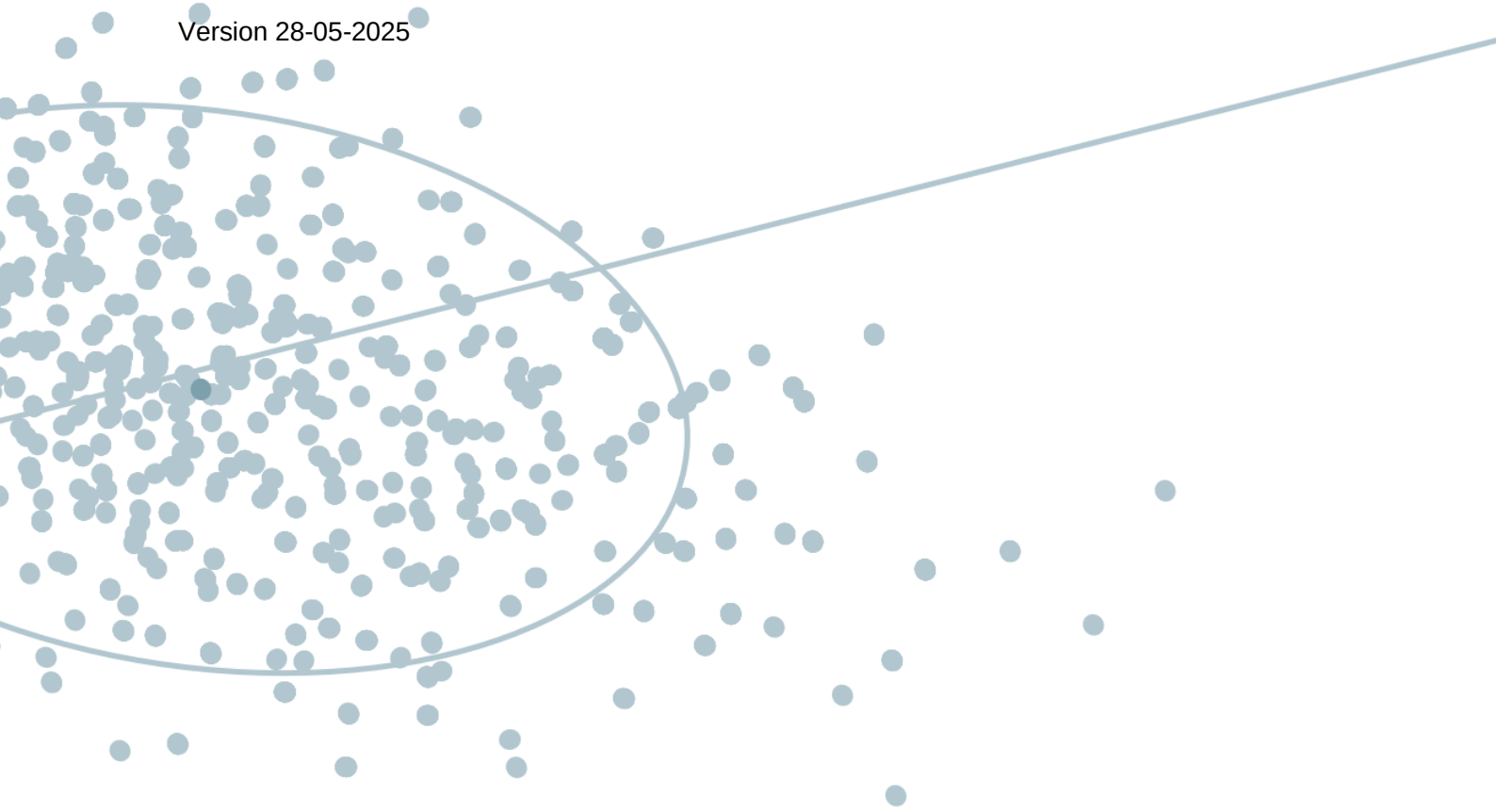

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| Title | Ginkgo biloba in patients with decreasing mental performance, peripheral arterial occlusive disease, vertigo, or tinnitus |
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**Conflict of Interest:**

All authors are employed by a healthcare consulting company that was contracted to complete this review. The authors have no financial, academic, personal, or any other conflicts of interest to declare in relation to this project.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

## Executive Summary

The herbal drug preparation ginkgo biloba is thought to reduce inflammation and improve cerebral blood flow; it is also thought to have antioxidant and neuroprotective effects. In Switzerland, ginkgo-based medicinal products have been approved and are reimbursed for adults with mental performance deficits (MPDs), peripheral arterial occlusive disease (PAOD), vertigo, and tinnitus. However, some studies have reported conflicting results regarding the effectiveness of this therapy. Within the context of the Federal Office of Public Health (FOPH) Health Technology Assessment (HTA) Program, the evidence for these coverage decisions is to be re-evaluated. This HTA protocol details the methodology for conducting an HTA report that will present all available evidence meeting the prespecified eligibility criteria on the use of ginkgo biloba for the abovementioned indications. The presented evidence is to inform policy makers in their decision if these drugs should continue to be reimbursed by the Swiss social health insurance.

A systematic literature review (SLR) adhering to international methodological standards will be conducted. MEDLINE, Embase, EconLit, CENTRAL, the Cochrane Database of Systematic Reviews (CDSR), and the National Health Service (NHS) Economic Evaluation Database (EED) (all via OvidSP), as well as the International Network of Agencies for Health Technology Assessment (INAHTA) database, will be searched to identify relevant studies. The SLR aims to identify evidence on the efficacy, effectiveness, and safety of ginkgo biloba in adults with MPDs, PAOD, vertigo, and tinnitus; each indication will be reviewed, analysed, and summarised separately. Searches of trial registries will also be conducted to capture ongoing randomised controlled trials (RCTs). The study design for the initial SLR is restricted to RCTs to inform the ***Efficacy*** chapter in the HTA report and comparative longitudinal observational studies to inform the ***Effectiveness*** chapter in the HTA report. The eligibility criteria will be expanded by descending the hierarchical evidence pyramid by study design, to provide additional evidence, if the evidence base is considered too sparse (<2 trials). The detailed methodology of this review will be outlined in the HTA report. Search strings consist primarily of terms related to the intervention of interest (ginkgo biloba) combined with study design terms. Screening will be conducted in 2 levels to include studies that meet the pre-defined study selection criteria: first, the title and abstract of each publication will be assessed for relevancy to the objectives of the SLR, and second, articles that seem to contain relevant data will undergo full-text screening. All screening will be performed by 2 independent reviewers. Data will be extracted from included publications by one reviewer and full data validation will be conducted by a second reviewer. The overall quality of evidence, for both RCTs and non-randomised studies, will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Studies with similar study design characteristics, intervention-comparator characteristics, and outcomes/endpoint characteristics will be included in meta-analyses. Results for all outcomes will be narratively synthesised.

A second SLR utilising the same databases, screening methodology, patient populations, and data extraction methodology will be conducted to identify economic evidence. Outcomes of interest include all-cause healthcare costs, disease-related healthcare costs, and outputs of economic evaluations, such as incremental cost-effectiveness ratios (ICERs). Cost-effectiveness analyses, budget impact models (BIMs), cost analyses, cost-utility analyses, cost-consequence analyses, cost-minimisation analyses, and cost-benefit analyses will be eligible for inclusion. The reporting quality of each economic evaluation will be assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Evidence from available health economic evaluations will be synthesised narratively and presented as tabular summaries.

To assess the total costs and budget impact of treatment with ginkgo biloba in patients with MPDs, PAOD, vertigo, or tinnitus, a BIM will be developed in accordance with appropriate guidelines. Outputs from the SLRs will be leveraged in the development of the BIM; where needed, targeted literature searches will be conducted to supplement gaps in data needed to inform the models.

For the evaluation of the ethical, legal, social and organisational domains, the publications included in the SLR will be reviewed for relevant issues and will be supplemented by a targeted literature search.

# Table of Contents

## Abbreviations and acronyms

| Abbreviation | Definition |
|---|---|
| 6MWD | 6-minute walk distance |
| 6MWT | 6-minute walk test |
| ABI | ankle-brachial index |
| ACD | absolute claudication distance |
| AChEIs | acetylcholinesterase inhibitors |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale-Cognitive |
| ADCS | Alzheimer's Disease Cooperative Study |
| ADLs | activities of daily living |
| AE | adverse event |
| BEHAVE-AD | Behavioral Pathology in Alzheimer's Disease Rating Scale |
| BIM | budget impact model |
| BMI | body mass index |
| BPPV | benign paroxysmal positional vertigo |
| CDSR | Cochrane Database of Systematic Reviews |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CHF | Swiss Franc |
| CI | confidence interval |
| CSF | cerebrospinal fluid |
| CVD | cardiovascular disease |
| DAD | Disability Assessment for Dementia |
| DHI | Dizziness Handicap Inventory |
| DLD | diffuse Lewy body disease |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5th edition |
| EED | Economic Evaluation Database |
| ELSO | ethical, legal, social or organisational |
| FCD | functional claudication distance |
| FOPH | Swiss Federal Office of Public Health |
| FTD | fronto-temporal dementia |
| FWD | functional walking distance |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |

| | |
|---|---|
| HMPC | Committee on Herbal Medicinal Products |
| HRQoL | health-related quality of life |
| HTA | health technology assessment |
| IADLs | instrumental activities of daily living |
| IC | intermittent claudication |
| ICD | initial claudication distance |
| ICER | incremental cost-effectiveness ratio |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| LY | life-year |
| MCI | mild cognitive impairment |
| MCS | Mental Component Summary |
| MD | mean difference |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MPD | mental performance deficit |
| MWD | maximum walking distance |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMDA | N-methyl-D-aspartate |
| NPI | neuropsychiatric inventory |
| OR | odds ratio |
| PAD | peripheral arterial disease |
| PAOD | peripheral arterial occlusive disease |
| PCS | Physical Component Summary |
| PDD | Parkinson disease dementia |
| PFWD | pain-free walking distance |
| PICO | population, intervention, comparator, and outcomes |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QoL-AD | Quality of Life-Alzheimer’s Disease |
| QoL-D | Quality of Life Questionnaire for Dementia |
| RCT | randomised controlled trial |
| SAE | serious adverse event |
| SF-36 | 36-Item Short Form Health Survey |

| | |
|---|---|
| SLR | systematic literature review |
| SMD | standardised mean difference |
| TFI | Tinnitus Functional Index |
| THI | Tinnitus Handicap Inventory |
| THQ | Tinnitus Handicap Questionnaire |
| TQ | Tinnitus Questionnaire |
| USA | United States of America |
| VAS | Visual Analogue Scale |
| VDADL | Vestibular Disorders Activities of Daily Living Scale |

## Objective of the HTA Protocol

Based on a preliminary screening of the literature the objective of the HTA protocol is to formulate the HTA key questions, to define the population, intervention, comparator, outcomes (PICO) and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the health technology assessment (HTA) report on the topic. Key questions are defined, addressing the main HTA domains, i.e. efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social and organisational issues.

# 1. Policy question and context

The HTA topic entails a policy question which will be informed by addressing HTA research questions (see ***Section 5***).

In healthcare, a policy question is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses uncertainty around a technology. This HTA report addresses the following policy question: does the existing evidence on efficacy, safety, appropriateness, and economic efficiency justify the coverage of ginkgo biloba for adults with mental performance deficits (MPDs), peripheral arterial occlusive disease (PAOD), vertigo, and/or tinnitus?

In Switzerland, ginkgo biloba is currently approved for coverage by the mandatory health insurance in a variety of formulations for the treatment of patients with MPDs, PAOD, vertigo, and tinnitus.[1] However, some studies have reported conflicting results regarding the effectiveness of this therapy. The Swiss Federal Office of Public Health (FOPH) is summoned to re-evaluate the evidence on ginkgo biloba. The HTA report following this HTA protocol will present all available evidence meeting prespecified eligibility criteria on the use of ginkgo biloba as a standalone therapy or as adjunctive treatment for MPDs, PAOD, vertigo, and tinnitus.

# 2. Medical background

## 2.1 MPD

Dementia—now referred to as major neurocognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)*—is an acquired disorder of cognitive functions (e.g. memory, social cognition, language, or perceptual-motor skills) due to brain dysfunction that consistently affects an individual's ability to perform daily activities. Dementia is an umbrella term for different diseases, such as Alzheimer's disease (AD) and vascular diseases, leading to MPD. Worldwide, almost 10 million people per year are diagnosed with dementia.[2] Clinically, dementia is characterised by a significant deterioration in one or more cognitive ability domains, namely learning and memory, social cognition, language, complex attention, executive functions, perceptual-motor function, and social cognition. Before receiving a dementia diagnosis, patients often experience a period of mild cognitive impairment (MCI), where the symptoms are present but daily life is not substantially affected, now referred to as minor neurocognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)*. In addition to clinical examination by a physician and a neuropsychological evaluation, diagnostic tools for dementia include neuroimaging, cerebrospinal fluid (CSF) and/or blood biomarkers (e.g. neurofilament light chain, plasma phosphorylated tau), and genetic markers to detect dementia-related cerebral changes or alternative explanations for the MPD.[3]

Although AD is the most condition leading to MPD, different types of brain pathology are found, such as tau and amyloid pathology in AD; tau-, FUS- or TDP43-pathology in fronto-temporal dementia (FTD), and synuclein pathology in Parkinson disease dementia (PDD) or diffuse Lewy body disease (DLD). Vascular pathology is the hallmark of vascular dementia but may also represent a co-factor in any other form of dementia. MPD may also be caused by other brain pathologies, such as traumatic brain injury, brain infections, or (non-progressive) stroke. Risk factors for MPDs include older age, smoking, arterial hypertension, and type 2 diabetes,[3] as well as low socio-economic status, hearing loss, and depression.[4]

By definition, the clinical course of dementia is progressive in nature. Although some dementia risk factors are modifiable, there is currently no cure for any dementia with neurodegenerative causes. Treatment options focus on lifestyle intervention, psychosocial support, and symptomatic management that aims to stabilise or ameliorate cognitive performance. With regard to AD dementia, pharmacological therapies include acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. In AD and PDD, AChEIs improve the functioning of cholinergic neurons and may stabilise or ameliorate memory functions but may also improve mood and behavioural changes. However, there are rarely cardiovascular and are frequently gastrointestinal adverse effects.[5] The NDMA receptor antagonist memantine is meant to achieve a neuroprotective effect against further nerve cell death in the brain, and may improve mood and behaviour in people with dementia due to AD.[6 7] However, patients may be likely to discontinue these treatments, with only about 40% (rivastigmine and galantamine) to 50% (donepezil and memantine) of patients continuing treatment for longer than 12 months.[8] Recent developments in pharmacotherapies for MCI due to AD and AD dementia show that lecanemab and other anti-amyloid monoclonal antibodies may slow the progression of cognitive decline compared to placebo.[3] These anti-amyloid antibodies clear the cerebral amyloid plaques, which are thought to play an important role in the pathogenesis of AD, and therefore may be able to target underlying causes rather than focusing on symptomatic management. However, the data that are currently available from clinical trials indicate that there is a considerable risk of adverse events with lecanemab and other anti-amyloid antibodies, in particular the so-called “amyloid-related imaging abnormalities”. Therefore, the possible risks of such therapies must be carefully balanced against the possible benefits.[3] Furthermore, uncertainties around pricing and the cost-effectiveness of lecanemab and other anti-amyloid antibodies mean that their role in treating AD remains unclear.[9 10]

In addition to these approved pharmacological therapies, patients with MPD of whatever cause may be treated with herbal medicinal products such as ginkgo biloba[11] or non-pharmacologic interventions such as cognitive stimulation[12] to help treat the symptoms of cognitive decline. Ginkgo biloba is believed to help treat symptoms of MCD primarily through its antioxidant effects,[13] but some preclinical evidence suggests that it also inhibits amyloid-β aggregation.[14]

## 2.2 PAOD

PAOD is a type of cardiovascular disease that affects the blood vessels in the limbs. It is typically caused by atherosclerosis, whereby blood flow to the extremities is restricted due to fatty deposits in the arteries.[15] [16] Risk factors include smoking, diabetes, body mass index (BMI) over 30, hypertension, dyslipidaemia, Black ethnicity, and family history of CVD.[17] The global prevalence of PAOD was estimated to be 6% in 2015.[18]

The most common symptom of PAOD is intermittent claudication (IC) – cramping and pain in the lower limbs during physical activity. Other symptoms include numbness in the legs, changes to the appearance of the skin, wounds and sores that do not heal, and brittle toenails.[19] In addition to physical examination of the lower limbs, the ankle-brachial index (ABI) test is used to diagnose PAOD by comparing blood pressure measurements from different parts of the body. Computed tomography or magnetic resonance imaging scans may also be required to establish a diagnosis of PAOD.[16] Improvement in either patient-reported symptoms, such as IC, or assessments by physicians, such as ABI, may be an indicator of treatment efficacy.

Without treatment, the progression of atherosclerosis in people with PAOD leads to a higher risk of coronary heart disease, stroke, and angina. Treatment is focused primarily on lowering cardiovascular risk factors through medical therapy (e.g. aspirin, statins, and anti-hypertension medication) and lifestyle changes, such as physical activity and giving up smoking.[20] However, introducing or increasing physical activity may be challenging due to the pain patients experience in PAOD. To combat this, patients may benefit from specialised exercise interventions that account for IC.[21] Patients may also receive herbal medicinal products such as ginkgo biloba, which may both treat the symptoms of PAOD and IC, as well as facilitate physical activity to help reduce cardiovascular risk factors.[22] Ginkgo biloba may treat PAOD symptoms through a variety of mechanisms, including antioxidant effects, vasodilation, and suppression of platelet activation.[23] [24] Where symptoms are severe, patients may be treated with angioplasty or stenting, bypass surgery, or limb amputation.[25]

## 2.3 Vertigo

Vertigo is a symptom that an individual experiences as a sensation of motion – most often a feeling of rotation or spinning – when they are not in motion. Other symptoms such as nausea, vomiting, and perspiration may also accompany the feeling of motion. It is estimated that approximately 3% to 10% of the population is affected by vertigo at some point during their lifetime.[26] In addition to having a negative impact on an individual's daily activities, vertigo increases the risk of falls, which may translate to a higher risk of injury in certain groups such as elderly people.[27] [28]

The aetiology of vertigo differentiates between peripheral and central vertigo. Diagnosing both types of vertigo entails a thorough physical examination, electrophysiological examination of the peripheral vestibular function, and eventually imaging studies of the brain undertaken in the case of suspected central vertigo.[29] [30] The causes of central vertigo include stroke, tumours, and other pathologies affecting the brainstem or cerebellum.[31] Peripheral vertigo is the more common type

and usually stems from vestibular disorders, whereby the sensory system that controls balance and co-ordination does not function properly. Benign paroxysmal positional vertigo (BPPV), Ménière's disease, and acute unilateral vestibulopathy (formerly called “vestibular neuronitis”) are among the underlying causes of peripheral vertigo.[32 33]

Treatment of vertigo depends on the identified underlying cause. Patients with central vertigo resulting from acute ischemic stroke affecting the brainstem or cerebellum may receive thrombolytic agents to dissolve blood clots and, in some cases, surgery may be necessary to relieve pressure on the brain.[34] Pharmacotherapy with 4-aminopyridine may also be beneficial for individuals with central vertigo.[35] Peripheral vertigo resulting from vestibular dysfunction can be treated with physical therapy and vestibular rehabilitation exercises, while pharmacological treatments such as antiemetics to combat nausea, anti-hypertension medication, antihistamines, and benzodiazepines can help to manage vertigo symptoms.[35 36] Although the specific mechanism through which ginkgo biloba may treat vertigo is not well understood, preclinical studies reported that ginkgo biloba may impact vestibular compensation, as demonstrated by an increase in both the new formation of synapses and protein synthesis in the vestibular nuclei.[37-39]

## 2.4 Tinnitus

Tinnitus is the symptom of hearing persistent sounds in the absence of an external auditory source. People with tinnitus compare the sounds that they hear to a variety of noises, such as ringing, buzzing, insects, winds, running water, grating metals, and running engines.[40] Based on a global SLR of 83 studies, the pooled prevalence of tinnitus among adults was 14.4% (range: 4.1% to 37.2%), and approximately 2.3% (range: 0.5% to 12.6%) of adults have severe tinnitus.[41] In addition, approximately 1% to 2% of the population perceive tinnitus to have a severely detrimental effect on their daily lives.[42] The underlying causes are extremely varied and include conditions related to the ear (e.g. sudden deafness, otitis, Ménière's disease, presbycusis, noise trauma), head and neck function (e.g. temporomandibular dysfunction, whiplash, cervicalgia),[43] neurologic causes (e.g. head injury), and side effects of medications; in many cases there is an interplay of various aetiologic factors and sometimes no clear underlying cause can be discerned.[40]

A diagnosis of tinnitus involves a comprehensive evaluation of the individual’s perception of the problem, possible sources of tinnitus-related distress, and comorbidities such as anxiety, insomnia, and head or neck pain, in addition to an audiological assessment.[44] A wide range of treatments to improve tinnitus symptoms have been studied, but the evidence base remains largely uncertain about their effectiveness; among these treatment options are antidepressants, betahistine (usually used as an anti-vertigo medication), ginkgo biloba, zinc, and transcranial stimulation.[44] Both animal and human studies indicate that ginkgo biloba acts through a variety of mechanisms, including antioxidant effects, suppression of platelet activation, and antiapoptotic activity. Although the precise mechanism has not been determined, these effects may work to help prevent free-radical damage to the cochlea, increase blood flow to the inner ear, and/or effect auditory processing.[37]

For people with hearing loss and tinnitus, amplification devices or cochlear implants may be considered.[44] Psychological interventions, such as tinnitus counselling, cognitive behavioural therapy, and mindfulness-based therapy may help to treat tinnitus-related distress and to reduce the negative impact of tinnitus on the individual's wellbeing through applying coping strategies and learning to live with the condition.[45] Cognitive behavioural therapy is the most well-researched treatment for tinnitus and is recommended by clinical practice guidelines, particularly among those with bothersome or severe tinnitus.[46-48]

# 3. Technology

## 3.1 Technology description

The herbal drug preparation ginkgo biloba consists of leaf extracts from the ginkgo biloba tree (also known as the maidenhair tree), most commonly found in eastern Asia. The main active ingredients from the leaf — terpene lactones and flavone glycosides — are used to create the standardised ginkgo extract EGb 761,[49] one of the most commonly used herbal drug preparations in the world.[50] The mechanism of action of ginkgo extract involves reducing inflammation and improving cerebral blood flow; it is also thought to have antioxidant and neuroprotective effects.[51]

The European Medicines Agency Committee on Herbal Medicinal Products (HMPC) developed an assessment report on the use of ginkgo biloba dry extract (drug-extract ratio 35-67:1),[52] as well as a European Union herbal monograph.[53] The HMPC monograph reports that the dry extract (drug-extract ratio 35-67:1) is appropriate for the improvement of age-associated cognitive impairment in daily dosages of 120 to 240 mg. Treatment should last at least 8 weeks; if symptoms have not improved within 3 months, clinicians should evaluate whether continued use is warranted. Although the HMPC report and monograph have not been updated since 2015, current clinical practice guidelines support the use of ginkgo biloba herbal medicinal products in patients with mild-to-moderate dementia.[54 55] In Switzerland, ginkgo-based products are approved and reimbursed either as standalone therapy or as adjunct treatment for patients with decreasing mental performance (after ruling out certain psychiatric or organic brain disorders requiring specific treatment), PAOD, vertigo, and tinnitus. The various formulations of ginkgo biloba that are reimbursed in Switzerland are detailed in ***Table 1***.

Ginkgo biloba is taken orally, either via capsules or tablets, in dosages of 120 to 240 mg per day.[1] The recommended duration of treatment is typically at least 8 weeks, with an assessment at 3 months to consider whether treatment continuation is appropriate. It should not be used in people with galactose intolerance or hypersensitivity to any of the ingredients. In some cases, ginkgo biloba lowers blood sugar levels, and in people with epilepsy, there is some risk of seizures being triggered by ginkgo extract.[1] There may be an interaction between ginkgo-based products and oral theophylline, efavirenz, medicines that inhibit blood clotting, and calcium antagonists.[1] Additionally, the efficacy of medications that involve cytochromes P450, 3A4, 1A2, 2E1, and 2C9 may be

affected by ginkgo extract. Due to a lack of available efficacy and safety evidence, ginkgo biloba is not currently recommended for use in children and adolescents. In addition, because it is unknown whether the ingredients of ginkgo-based products pass into breast milk, ginkgo biloba should be avoided while breastfeeding. Although there is no evidence of reproductive toxicity, ginkgo-based products may impact bleeding and are therefore not recommended for use during pregnancy.[1]

**Table 1: Indications**

| Formulation | Indication(s) | Route of administration | Dosing |
|---|---|---|---|
| SimiMed Ginkgo | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC, vertigo, and tinnitus | Tablet | 2 x 120 mg or 1 x 240 mg per day |
| Ginkgo-Mepha | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC, vertigo, and tinnitus | Tablet (80 mg or 120 mg) | 120-240 mg per day divided into 2 or 3 doses |
| Ginkgo Sandoz® | • Symptomatic treatment of MPD<br>• Dizziness of unknown cause | Tablet (80 mg or 120 mg) | 240 mg per day divided into 2 or 3 doses |
| Ginkgo Spirig HC® | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 1 x 240 mg or 2 x half 240 mg tablet |
| Rezirkane® | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 120-240 mg daily in 1-2 single doses |
| Symfona® 120 mg | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Capsule | 2 x 120 mg per day |
| Symfona® 240 mg | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 1 x 240 mg per day |
| Tebokan® 120 | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Tablet | 2 x 120 mg per day |

| Formulation | Indication(s) | Route of administration | Dosing |
|---|---|---|---|
| Tebokan® 240 | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Tablet | 1 x 240 mg per day |

*Abbreviations*

IC = intermittent claudication, MPD = mental performance deficits

*Notes*

**Source:** Medicinal product information search platform (AIPS) (Drug Information Publication System FI/PI)[1]

# 4. Population, intervention, comparator, and outcomes (PICO)

PICO criteria for this HTA are defined below and summarised in ***Table 2***.

## 4.1 Population

### 4.1.1 MPD

Eligible studies include adults currently experiencing MPDs of varying degrees of severity including MCI and sub-types of dementia such as AD, PDD, DLD, FTD, and vascular dementia. MPDs can have various aetiologies and are very broadly defined in the literature. Detailed information about the type and severity of MPD for each included study will be recorded and used to group studies of similar patients for synthesis. Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both MPDs and hypertension) will only be included if there are no available studies on MPDs alone.

### 4.1.2 PAOD

Eligible studies include adults with PAOD, sometimes also referred to as peripheral arterial disease (PAD). Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both PAOD and acute myocardial infarction) will only be included if there are no available studies on PAOD alone.

### 4.1.3 Vertigo

Eligible studies include adults who experience vertigo and/or dizziness (peripheral or central vestibular system dysfunction).[A] Vertigo may be a symptom of other underlying conditions, such as multiple sclerosis or vestibular migraine. The underlying condition of patients in the originally

[A] This includes acute vestibular syndrome (i.e. usually manifests with a single episode, such as vestibular neuritis), episodic vestibular syndrome (i.e. recurrent by nature, such as Ménière's disease or vestibular migraine), and chronic vestibular syndrome (i.e. persistent symptoms over an extended period of time, such as cerebellar degeneration).

included studies, if applicable, will be recorded and used to group similar patients. Studies including only patients with a specific subtype of vertigo (i.e. peripheral vertigo or central vertigo alone) are eligible. Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both vertigo and hypertension) will only be included if there are no available studies on vertigo alone.

#### 4.1.4 Tinnitus

Eligible studies include adults with tinnitus.[B] Studies including only patients with a specific subtype of tinnitus (e.g. acute tinnitus alone) are eligible. Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both tinnitus and depression) will only be included if there are no available studies on tinnitus alone.

### 4.2 Intervention

The intervention of interest is any formulation of ginkgo biloba that is an approved and reimbursed herbal medicinal product in Switzerland (Table 1). Because patients with the conditions of interest may be receiving other treatments, studies in which ginkgo biloba is evaluated together with another intervention (i.e. standard of care) are eligible as long as these co-interventions are identical across treatment arms and approved in Switzerland.

### 4.3 Comparators

Eligible comparators include placebo, no treatment, and standard of care, as described below:

**Placebo:** An oral placebo is a pharmaceutically inert substance, usually a sugar pill, often given to patients within a randomised controlled trial (RCT) to help control for any effects not due to the actual pharmacological mechanism of the treatment under investigation.[56 57]

**No treatment:** No intervention given to patients.

**Standard of care/active treatment:** Medications may be used to treat the underlying disease or symptoms (e.g. donepezil, rivastigmine, or galantamine for dementia due to AD).[1] In addition, non-pharmacological treatments, such as cognitive stimulation, tinnitus retraining therapy, or physical exercise programs, may be used alone or in conjunction with pharmacological interventions.[12 21 58]

Any of the comparators described above may also be compared with ginkgo biloba in studies with a backbone treatment, provided that the backbone treatment is identical across treatment arms (e.g. a study of ginkgo plus backbone treatment vs. placebo plus backbone treatment).

[B] This includes acute tinnitus (duration less than 3 months), chronic tinnitus (duration of more than 3 months), and sub-acute tinnitus (although this term is rarely used, studies describing patients with sub-acute tinnitus will be included so that the review is comprehensive).

## 4.4 Outcomes

During the screening and data extraction process, the questionnaires and collection methods used to assess each outcome will be captured and results data will be extracted and synthesised. Based on data from RCTs included in existing systematic literature reviews (SLRs) conducted by Cochrane and others,[11 12 21 22 37 58-66] commonly used outcomes have been described below. Although several questionnaires used to collect outcomes are described below, all questionnaires for each outcome are eligible for inclusion (e.g. questionnaires on cognitive function that are not described below are eligible).

### 4.4.1 MPD

#### 4.4.1.1 Cognitive function

Cognitive function and cognitive decline may be assessed using a variety of general and disease-specific tools. Some disease-specific tools have only been validated in the population for which they were originally developed, while others have been utilised in broader populations. The tools listed below are typically used to assess cognitive function in patients with MPDs.[11 12 62 64]

- Mini-Mental State Examination (MMSE): The MMSE is a short questionnaire typically administered by a healthcare professional that assesses several aspects of a patient's cognitive performance, including their orientation, memory, attention, and ability to follow verbal and written commands. Scores range from 0 to 30, with higher scores indicating better cognitive performance.[67] MMSE is a validated tool in the assessment of AD but is less suited to assess patients with fronto-temporal and/or executive dysfunctions (e.g. in PDD, DLD, and FTD).
- Montreal Cognitive Assessment (MoCA): MoCA is a brief screening tool for the assessment of cognitive functions administered by a certified tester. Total scores range from 0 to 30 (higher scores indicate better cognitive performance) and include several domains: executive functioning and visuospatial skills (5 points); language and naming (6 points); memory (5 points); attention and concentration (6 points); abstraction (2 points); and orientation (6 points). Using the suggested cut-off, a score of less than 26 is indicative of MCI.[68 69] MoCa is a validated tool in AD, but is also suited to assess patients with fronto-temporal and/or executive dysfunctions such as in PDD, DLD or FTD.
- Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog): Although the ADAS-cog was developed for AD, it has since been used in populations with related conditions, including Parkinson's disease dementia. The original ADAS-cog combines the scores from 11 components (word recall, word recognition, constructional praxis, orientation, naming objects and fingers, commands, ideational praxis, remember test instruction, spoken language, word finding, and comprehension). Scores range from 0 to 70, with lower scores indicating better cognitive functioning.[70 71]

#### 4.4.1.2 Behavioural changes

Studies may assess general behaviour rating or utilise scales that focus on specific behavioural challenges. The tools listed below are typically used to assess behaviour in patients with MPDs.[12]

- Neuropsychiatric Inventory (NPI): The NPI assesses the frequency and severity of symptoms of psychopathology. The original NPI included 10 symptom domains (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour); 2 additional domains (sleep disturbances and appetite disturbances) were added later. The total score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense symptoms.[72]
- Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): BEHAVE-AD includes 25 symptoms, each scored from 0 (not present) to 3 (present, generally with an emotional and physical component). These 25 symptoms cover 7 domains: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties and phobias.[73]

#### 4.4.1.3 Functional status

Functional status is primarily assessed through questionnaires on the activities of daily living (ADLs) or instrumental ADLs (IADLs). Both general and disease-specific tools have been used. Because MPDs can have various aetiologies and may be very broadly defined in the literature, it is likely that disease-specific tools are used inconsistently across eligible studies. However, disease-specific tools may still provide relevant information, particularly if sufficient data are available on specific conditions. The tools described below are typically used to assess functional status in patients with MPDs.[11 12 64]

- Alzheimer's Disease Cooperative Study-ADL Scale (ADCS-ADL): The ADCS-ADL consists of 23 questions that assess participants' independence when completing activities such as eating, hygiene practices, hobbies, and appointments. Higher scores (possible range: 0 to 78) indicate better functional status.[74]
- ADCS-ADL adapted for MCI (ADCS-MCI-ADL): The ADCS-MCI-ADL was adapted from its parent questionnaire, the ADCS-ADL, to be more suitable for patients with MCI and is available as either an 18- or 24-question scale. Compared to the ADCS-ADL, the ADCS-MCI-ADL focuses more on IADLs, such as balancing a checkbook, shopping, and meal preparation, rather than basic ADLs such as bathing. Scores range from 0 to either 53 (18-question scale) or 69 (24-question scale), and higher scores indicate better functional status.[75]
- Disability Assessment for Dementia (DAD): The DAD includes 40 items related to basic self-care (17 items) and IADLs (23 items). Each item is rated as "no" (patient has not performed the activity without help/reminders in the past 2 weeks), "yes" (patient has performed the activity without help/reminders in the past 2 weeks) or not applicable (e.g.

patient did not have the opportunity to perform this activity). The total score is calculated as a percentage of "yes" answers out of the total number of applicable items (e.g. if 2 questions were not applicable and 33 questions were answered "yes," the total score is 33/38, or 83%).[76]

#### 4.4.1.4 Health-related quality of life (HRQoL)

HRQoL may be assessed using both general and disease-specific tools. Because MPDs can have various aetiologies and may be very broadly defined in the literature, it is likely that disease-specific tools are used inconsistently across eligible studies. However, disease-specific tools may still provide relevant information, particularly if sufficient data are available on specific conditions. The most common HRQoL assessment tools for the patient population in this report are described below.[12 62]

- EQ-5D: The EQ-5D assesses general HRQoL using 2 scores. The EQ-5D index score ranges from 0 to 1 (higher indicates better HRQoL) and is derived from patients' rating each of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as no problems, some problems, or extreme problems. The EQ-5D visual analogue scale (VAS) asks patients to mark their own perceived health state on a 20 cm line in which 0 is described as the "worst imaginable health state" and 100 is the "best imaginable health state."[77]
- SF-36: The SF-36 is a questionnaire that uses 36 items to assess general HRQoL. Patient responses are combined to create 8 sub-scale scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 summary scores (Physical Component Summary [PCS] and Mental Component Summary [MCS]). Each score is transformed to range from 0 to 100, with higher scores indicating better HRQoL.[78 79]
- Quality of Life-Alzheimer's Disease (QoL-AD): QoL-AD was developed to assess HRQoL in patients with AD based on responses from patients and caregivers. The patient and their caregiver (s) assess each of 13 items on a scale of 1 (poor) to 4 (excellent). Total scores range from 13 to 52, with higher scores indicating better HRQoL.[80]
- Quality of Life Questionnaire for Dementia (QoL-D): QoL-D uses 29 items, each rated on either frequency or enjoyment from 1 (frequency: never; enjoyment: not at all) to 5 (frequency: very often; enjoyment: very), to assess HRQoL in patients with dementia. Each item contributes to one of 5 scores: self-esteem, positive affect/humour, negative affect, feelings of belonging, and sense of aesthetics. Each score ranges from 1 to 5, with higher scores indicating better HRQoL.[81]

#### 4.4.1.5 Adverse events (AEs)/serious adverse events (SAEs)

- AEs, which are unfavourable outcomes that occur during or after receipt of a medical intervention, may be collected in a variety of ways. In RCTs, they are most commonly collected passively, with patients bringing new symptoms to healthcare professionals as they occur. They may also be collected actively, utilising questionnaires (e.g. asking patients which of a list of symptoms they have experienced in the last week), physical examinations (e.g. weight or blood pressure measurements), or laboratory tests (e.g. blood glucose tests). This SLR will extract data on all reported AEs, including but not limited to the number of patients experiencing any AE, the number of patients experiencing any SAE, treatment discontinuation due to AEs, and specific AEs such as nausea, headaches, or low blood sugar. Although SAEs are inconsistently defined across national regulatory agencies, they generally include AEs that are life-threatening, require hospitalisation, result in death, disability, or a congenital anomaly, or require medical or surgical intervention to prevent one of the above. The specific definition of SAEs used in each included study will be captured during data extraction (where reported) to assess when synthesis across studies is appropriate.[82]

#### 4.4.1.6 Economic outcomes

- All-cause healthcare costs: Any type of direct healthcare costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs for any reason.
- Disease-related healthcare costs: Any type of direct healthcare costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs due to causes related to the condition under study.
- Data reported in economic evaluations: Outputs, including but not limited to incremental and total costs, incremental and total effects, life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs).
- Budget impact: Economic outcomes will be utilised to inform a budget impact model (BIM), described in ***Section 6.3***.

### 4.4.2 PAOD

#### 4.4.2.1 Mobility

PAOD often results in lower limb pain that may interfere with mobility. In this patient population, mobility is typically assessed using a physical test of walking capability, rather than a questionnaire.[21 22 59 63]

- Absolute claudication distance (ACD; also called maximum walking distance [MWD]): ACD is the maximum distance that a person can walk before intolerable claudication pain forces them to stop. ACD is typically measured using a treadmill.[83]
- Functional claudication distance (FCD; also called functional walking distance [FWD]): FCD is the maximum distance that a person can walk before they would prefer to stop because of claudication pain. FCD is typically measured using a treadmill.[83 84]
- Initial claudication distance (ICD; also called or pain-free walking distance [PFWD]): ICD is the maximum distance that a person can walk before they begin experiencing claudication pain. ICD is typically measured using a treadmill.[84]
- Six-minute walk test (6MWT): The 6MWT is a test to measure the total distance that a person can walk in 6 minutes (6-minute walk distance [6MWD]). The 6MWT can be administered using a treadmill or in a 100-meter section of a straight hallway with a smooth floor.[85]

#### 4.4.2.2 Pain

The most common symptom of PAOD is IC, or muscle pain in the leg that occurs during exercise. This pain is typically relieved by rest. In this patient population, pain was rarely reported, but it was consistently assessed with a VAS.[22]

- VAS: The VAS is a single item used to assess pain. It is typically presented as a 10 cm vertical line, although other orientations and lengths have been used. Patients are asked to mark their level of pain on a scale that ranges from "no pain" to "worst pain ever."[86 87]

#### 4.4.2.3 Peripheral blood circulation

Peripheral blood circulation was most commonly assessed using the ABI, although a small number of RCTs did report blood pressure taken at the ankle or calf.[22 59 63]

- ABI: The ABI is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. Because of the intra- and interobserver variability inherent to blood pressure measurement, limb pressure should be measured twice and averaged to improve precision. The recommended threshold for diagnosing PAOD is an ABI value of 0.90 or below. A decrease in ABI of at least 0.15 indicates disease progression.[88]

#### 4.4.2.4 HRQoL

HRQoL may be assessed using both generic and disease-specific tools. The most typical generic tools are described below.[21 22 59 63] Please note that the generic HRQoL tools described below are the same as those described in the corresponding sections of the other conditions of interest, although other sections may contain additional disease-specific tools.

- EQ-5D: The EQ-5D assesses general HRQoL using 2 scores. The EQ-5D index score ranges from 0 to 1 (higher indicates better HRQoL) and is derived from patients' rating each of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)

as no problems, some problems, or extreme problems. The EQ-5D VAS asks patients to mark their own perceived health state on a 20 cm line in which 0 is described as the "worst imaginable health state" and 100 is the "best imaginable health state."[77]

- SF-36: The SF-36 is a questionnaire that uses 36 items to assess general HRQoL. Patient responses are combined to create 8 sub-scale scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 summary scores (PCS and MCS). Each score is transformed to range from 0 to 100, with higher scores indicating better HRQoL.[78 79]

#### 4.4.2.5 AEs/SAEs

- AEs, which are unfavourable outcomes that occur during or after receipt of a medical intervention, may be collected in a variety of ways. In RCTs, they are most commonly collected passively, with patients bringing new symptoms to healthcare professionals as they occur. They may also be collected actively, utilising questionnaires (e.g. asking patients which of a list of symptoms they have experienced in the last week), physical examinations (e.g. weight or blood pressure measurements), or laboratory tests (e.g. blood glucose tests). This SLR will extract data on all reported AEs, including but not limited to the number of patients experiencing any AE, the number of patients experiencing any SAE, treatment discontinuation due to AEs, and specific AEs such as nausea, headaches, or low blood sugar. Although SAEs are inconsistently defined across national regulatory agencies, they generally include AEs that are life-threatening, require hospitalisation, result in death, disability, or a congenital anomaly, or require medical or surgical intervention to prevent one of the above. The specific definition of SAEs used in each included study will be captured during data extraction (where reported) to assess when synthesis across studies is appropriate.[82] Please note that this information about AEs is the same as described in the corresponding sections of the other conditions of interest.

#### 4.4.2.6 Economic outcomes

Please note that the economic outcomes described below are identical to those described in the corresponding sections of the other conditions of interest.

- All-cause healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs for any reason.
- Disease-related healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs due to causes related to the condition under study.

- Data reported in economic evaluations: Outputs, including but not limited to incremental and total costs, incremental and total effects, LYs, QALYs, and ICERs.
- Budget impact: Economic outcomes will be utilised to inform a BIM, described in **Section 6.3**.

### 4.4.3 Vertigo

4.4.3.1 Timing and intensity of vestibular symptoms, including patient-perceived handicap

In addition to assessing and reporting the intensity, frequency, and duration of episodes separately, investigators may utilise validated scales to assess patients' overall experience of vertigo symptoms (including intensity, frequency, and duration of episodes).[61 65]

- Count of episodes per time period
- Single question ordinal scale to assess intensity
- Mean/median duration of episode
- Dizziness Handicap Inventory (DHI): For each of the 25 items on the DHI questionnaire, patients select the statement that applies most to them from 3 choices (score of 0, 2, or 4). The possible total score ranges from 0 to 100, where higher scores indicate a worse handicap associated with dizziness. This scoring is in contrast to the DHI short form, in which this score ranges from 0 to 13 and lower scores indicate a worse handicap associated with dizziness.[89]
- Vestibular Disorders Activities of Daily Living Scale (VDADL): On the VDADL, patients rate each of 28 items from 1 (I am not disabled, perceive no change in performance from before developing an inner ear impairment) to 10 (I no longer perform the activity due to vertigo or a balance problem). The summary score for the VDADL is the median score across the 28 items, and also ranges from 1 to 10, with higher scores indicating more severe impairment due to vertigo.[90]

4.4.3.2 HRQoL

HRQoL may be assessed using both generic and disease-specific tools. The most typical generic tools are described below.[61 65] Please note that the generic HRQoL tools described below are the same as those described in the corresponding sections of the other conditions of interest, although other sections may contain additional disease-specific tools.

- EQ-5D: The EQ-5D assesses general HRQoL using 2 scores. The EQ-5D index score ranges from 0 to 1 (higher indicates better HRQoL) and is derived from patients' rating each of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as no problems, some problems, or extreme problems. The EQ-5D VAS asks patients to mark their own perceived health state on a 20 cm line in which 0 is described as the "worst imaginable health state" and 100 is the "best imaginable health state."[77]

- SF-36: The SF-36 is a questionnaire that uses 36 items to assess general HRQoL. Patient responses are combined to create 8 sub-scale scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 summary scores (PCS and MCS). Each score is transformed to range from 0 to 100, with higher scores indicating better HRQoL.[78] [79]

#### 4.4.3.3 AEs/SAEs

- AEs, which are unfavourable outcomes that occur during or after receipt of a medical intervention, may be collected in a variety of ways. In RCTs, they are most commonly collected passively, with patients bringing new symptoms to healthcare professionals as they occur. They may also be collected actively, utilising questionnaires (e.g. asking patients which of a list of symptoms they have experienced in the last week), physical examinations (e.g. weight or blood pressure measurements), or laboratory tests (e.g. blood glucose tests). This SLR will extract data on all reported AEs, including but not limited to the number of patients experiencing any AE, the number of patients experiencing any SAE, treatment discontinuation due to AEs, and specific AEs such as nausea, headaches, or low blood sugar. Although SAEs are inconsistently defined across national regulatory agencies, they generally include AEs that are life-threatening, require hospitalisation, result in death, disability, or a congenital anomaly, or require medical or surgical intervention to prevent one of the above. The specific definition of SAEs used in each included study will be captured during data extraction (where reported) to assess when synthesis across studies is appropriate.[82] Please note that this information about AEs is the same as described in the corresponding sections of the other conditions of interest.

#### 4.4.3.4 Economic outcomes

Please note that the economic outcomes described below are identical to those described in the corresponding sections of the other conditions of interest.

- All-cause healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs for any reason.
- Disease-related healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs due to causes related to the condition under study.
- Data reported in economic evaluations: Outputs including but not limited to incremental and total costs, incremental and total effects, LYs, QALYs, and ICERs.
- Budget impact: Economic outcomes will be utilised to inform a BIM, described in ***Section 6.3***.

### 4.4.4 Tinnitus

#### 4.4.4.1 Tinnitus severity

Typical tools used to assess tinnitus severity are listed below.[58 60 66 91]

- Tinnitus Handicap Inventory (THI): Patients report whether each of the 25 items on the THI is a problem caused by their tinnitus (yes, sometimes, or no). The items are combined to create a total score (range: 0 to 100), as well as scores for functional (range: 0 to 44), emotional (range: 0 to 36), and catastrophic (range: 0 to 20) subscales. For all scales, higher scores indicate a higher perceived handicap due to tinnitus.[92]
- Tinnitus Handicap Questionnaire (THQ): The THQ is a 27-item questionnaire based on problems that patients with tinnitus rated as important. Patients rate each question from 0 (no handicap) to 100 (severe handicap). The results are summarised in a total score, Factor 1 score (social, emotional, and behavioural effects), and Factor 2 score (tinnitus and hearing).[93]
- Tinnitus Questionnaire (TQ): The TQ is a 52-item questionnaire assessing tinnitus-related distress. Each item is rated as 0 (true), 1 (partly true) or 2 (not true), with higher scores indicating more distress. The total score (range: 0 to 84) combines 40 of the 52 items (2 items are double counted). Items are also combined to create subscales for emotional distress (range: 0 to 24), cognitive distress (range: 0 to 16), intrusiveness (range: 0 to 16), auditory perceptual difficulties (range: 0 to 14), sleep disturbances (range: 0 to 8), and somatic complaints (range: 0 to 6).[94-96]
- Tinnitus Functional Index (TFI): The TFI is a questionnaire with 25 items; 23 of these questions are rated from 0 to 10, while the remaining 2 questions are rated from 0% to 100% in 10-point increments (higher scores indicate higher levels of severity for all questions). These questions are transformed and combined to create an overall score and 8 subscales (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotional), all ranging from 0 to 100.[97]

#### 4.4.4.2 Tinnitus loudness

Typical tools to assess tinnitus loudness are listed below.[58]

- Audiometric loudness matching: In audiometric loudness matching, sounds that best match the quality and pitch of the tinnitus are played in the opposite ear, and the patient adjusts the intensity or loudness (either directly or indirectly) until the sound being played matches the tinnitus. However, this method may be challenging when tinnitus is binaural or when the sound varies in quality and/or pitch.[98]
- VAS: The VAS is a single item used to assess tinnitus loudness. It is typically presented as a 10 cm vertical line, although other orientations and lengths have been used. Patients are asked to mark the level of tinnitus loudness they are currently experiencing. Although this

is often used to assess tinnitus loudness, it may also be affected by how a person is impacted by their tinnitus.[99]

#### 4.4.4.3 Level of hearing loss

Audiometry, testing carried out by trained personnel, is considered the gold standard to assess level of hearing loss.[100 101] Pure-tone audiometry assesses patients' ability to hear tones played for them, both across and beyond the speech spectrum, at various volume levels to determine the limits of patients' hearing.[102] Hearing loss may also be assessed using self-report.[100 101]

#### 4.4.4.4 HRQoL

HRQoL may be assessed using both generic and disease-specific tools. The most typical generic tools are described below.[58 66 91] Please note that the generic HRQoL tools described below are the same as those described in the corresponding sections of the other conditions of interest, although other sections may contain additional disease-specific tools.

- EQ-5D: The EQ-5D assesses general HRQoL using 2 scores. The EQ-5D index score ranges from 0 to 1 (higher indicates better HRQoL) and is derived from patients' rating each of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as no problems, some problems, or extreme problems. The EQ-5D VAS asks patients to mark their own perceived health state on a 20 cm line in which 0 is described as the "worst imaginable health state" and 100 is the "best imaginable health state."[77]
- SF-36: The SF-36 is a questionnaire that uses 36 items to assess general HRQoL. Patient responses are combined to create 8 sub-scale scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 summary scores (PCS and MCS). Each score is transformed to range from 0 to 100, with higher scores indicating better HRQoL.[78 79]

#### 4.4.4.5 AEs/SAEs

- AEs, which are unfavourable outcomes that occur during or after receipt of a medical intervention, may be collected in a variety of ways. In RCTs, they are most commonly collected passively, with patients bringing new symptoms to healthcare professionals as they occur. They may also be collected actively, utilising questionnaires (e.g. asking patients which of a list of symptoms they have experienced in the last week), physical examinations (e.g. weight or blood pressure measurements), or laboratory tests (e.g. blood glucose tests). This SLR will extract data on all reported AEs, including but not limited to the number of patients experiencing any AE, the number of patients experiencing any SAE, treatment discontinuation due to AEs, and specific AEs such as nausea, headaches, or low blood sugar. Although SAEs are inconsistently defined across national regulatory agencies, they generally include AEs that are life-threatening, require hospitalisation, result in death, disability, or a congenital anomaly, or require medical or surgical intervention to prevent one of the above. The specific definition of SAEs used in each included study will be captured

during data extraction (where reported) to assess when synthesis across studies is appropriate.[82] Please note that this information about AEs is the same as described in the corresponding sections of the other conditions of interest.

#### 4.4.4.6 Economic outcomes

Please note that the economic outcomes described below are identical to those described in the corresponding sections of the other conditions of interest.

- All-cause healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs for any reason.
- Disease-related healthcare costs: Any type of direct costs, including but not limited to inpatient, outpatient, emergency department, other medical care such as nursing care, diagnostic tests or imaging, and pharmacy costs, that a patient incurs due to causes related to the condition under study.
- Data reported in economic evaluations: Outputs including but not limited to incremental and total costs, incremental and total effects, LYs, QALYs, and ICERs.
- Budget impact: Economic outcomes will be utilised to inform a BIM, described in ***Section 6.3***.

**Table 2: PICO**

| | | | | |
|---|---|---|---|---|
| **P:** | Adults with MPDs. MPDs are symptoms with varying aetiologies, including but not limited to neurodegenerative AD, PDD, DLD, FTD, and vascular dementia. | Adults with PAOD, also known as PAD. | Adults with vertigo/dizziness (peripheral or central vestibular system dysfunction). This includes acute vestibular syndrome (i.e. usually manifests with a single episode, such as vestibular neuritis), episodic vestibular syndrome (i.e. recurrent by nature, such as Ménière's disease or vestibular migraine), and chronic vestibular syndrome (i.e. persistent symptoms over an extended period of time, such as cerebellar degeneration). | Adults with tinnitus, including acute tinnitus (duration <3 months), chronic tinnitus (duration >3 months), and sub-acute tinnitus (although this term is rarely used, for completeness, studies describing patients with sub-acute tinnitus are eligible). |
| **I:** | Ginkgo biloba<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | | | |
| **C:** | • Placebo<br>• No treatment<br>• Standard of care | | | |
| **O:** | • Cognitive function<br>• Behavioural changes<br>• Functional status | • Mobility<br>• Pain<br>• Peripheral blood circulation | • Timing and intensity of vestibular symptoms, including patient-perceived handicap | • Tinnitus severity<br>• Tinnitus loudness<br>• Level of hearing loss |

| | | | | |
|---|---|---|---|---|
| | • HRQoL<br>• All AEs/SAEs<br>• Economic outcomes | • HRQoL<br>• All AEs/SAEs<br>• Economic outcomes | • HRQoL<br>• All AEs/SAEs<br>• Economic outcomes | • HRQoL<br>• All AEs/SAEs<br>• Economic outcomes |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, C = comparator, HRQoL = health-related quality of life, I = intervention. MCI = mild cognitive impairment, MPD = mental performance deficits, O = outcome, P = population, PAD = peripheral arterial disease, PAOD = peripheral arterial occlusive disease, SAE = serious adverse event

# 5. HTA research questions

## 5.1 HTA research questions

For the evaluation of the technology the following research questions are addressed:

1. Is the technology effective/efficacious compared to the comparator technology?
2. Is the technology safe compared to the comparator technology?
3. What is the budget impact of the technology?
4. What is the cost-effectiveness of the technology?
5. Are there ethical, legal, social or organisational (ELSO) issues related to the technology?

# 6. Methodology

## 6.1 Systematic literature review of clinical evidence

### 6.1.1 Databases and search strategy

The SLR will be conducted in accordance with guidance from the Cochrane Handbook for Systematic Reviews of Interventions[103] and the reporting will consider all items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[104] The search parameters for the identification of relevant literature are detailed in ***Table 3***. The search strategies have been developed based on the PICO framework, in cooperation with an information specialist and taking the European Union herbal monograph on Ginkgo biloba L., folium into account.[53] The search strategies will use Medical Subject Headings and Emtree terms, as well as free-text words specific to the research questions being addressed. Because MPDs can have varying aetiologies and are described using many different terms in the literature, the search strategy does not include population terms. Instead, the search strategy aims to identify all records reporting on any clinical outcomes from observational or interventional studies. The full search strategies are presented in ***Appendix A***. To gain insight into ongoing RCTs with study characteristics aligned with the PICO of this HTA, supplementary searches will be conducted on the websites of ClinicalTrials.gov (https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu). Where trial registrations can be matched to published trials, the registration will be utilised to assess selective outcome reporting. In addition to controlled studies, uncontrolled observational studies will be identified through published SLRs and monographs.

**Table 3: Search parameters**

| | |
|---|---|
| **Electronic databases** | MEDLINE, Embase, EconLit, CENTRAL, CDSR, and NHS EED (all via OvidSP); INAHTA |
| **Other sources** | • ClinicalTrials.gov (https://clinicaltrials.gov) https://clinicaltrials.gov<br>• European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu) https://www.clinicaltrialsregister.eu<br>• Reference lists of relevant published SLRs/meta-analyses identified in the database search |
| **Publication type** | Journal articles only |
| **Search dates** | No restriction |
| **Language** | No restriction[a] |
| **Geography** | No restriction |

*Abbreviations*

CDSR = Cochrane Database of Systematic Reviews, EED = Economic Evaluation Database, INAHTA – International Network of Agencies for Health Technology Assessment, NHS = National Health Service, SLR = systematic literature review

*Notes*

a = Although the search strategy will not be restricted by language, publications in languages other than English, German, Italian, and French will be excluded during title/abstract screening.

### 6.1.2 Study selection

The electronic records of the articles retrieved by the database searches will be exported into an EndNote library (Clarivate Analytics, United States of America [USA]), and after deduplication, they will be imported into DistillerSR for study selection. DistillerSR is an online tool that allows for blinded title/abstract and full-text screening of citations between independent reviewers and resolution of study inclusion conflicts. Screening will be performed to include studies that meet the pre-defined study selection criteria (***Table 4*****,** ***Table 5*****,** ***Table 6*****,** and ***Table 7***), as well as to provide an exclusion reason for each publication/study that does not meet at least one of the pre-defined criteria. Screening will be conducted in 2 levels: first, the title and abstract of each publication will be assessed for relevancy to the objectives of the SLR; second, articles that seem to contain relevant data will undergo full-text screening.

The identified title/abstracts and full-text publications will be screened by 2 independent reviewers, and conflicts will be resolved via discussion. If a consensus cannot be reached, a third reviewer will be consulted. SLRs/meta-analyses of relevant populations identified via the database search will be flagged during the screening process and utilised to identify any additional studies. The studies included in such SLRs/meta-analyses will be compared with the final list of included studies in this SLR to determine if any additional studies are eligible.

## Table 4: Eligibility criteria: Clinical evidence for MPD

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with MPDs. MPDs are symptoms with varying aetiologies, including but not limited to neurodegenerative AD, PDD, DLD, FTD, or vascular dementia | • Patients without MPDs (e.g. taking ginkgo biloba preventively)<br>• Studies in which not all patients have MPDs and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both MPDs and hypertension)[b] |
| **Interventions** | Ginkgo biloba<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions, including herbal supplements or other formulations of ginkgo biloba[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Standard of care | Other comparators[c] |
| **Outcomes** | • Cognitive function<br>• Behavioural changes<br>• Functional status<br>• HRQoL<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f]<br>• Comparative longitudinal observational studies[f] | • Comparative cross-sectional studies[f]<br>• Single-arm clinical or observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, DLD = diffuse Lewy body disease, FTD = fronto-temporal dementia, MCI = mild cognitive impairment, HRQoL = health-related quality of life, MPD = mental performance deficit, PDD = Parkinson disease dementia, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review

*Notes*

a = Studies in which only a subset of patients meets the relevant eligibility criteria (e.g. some do not have MPD or are younger than 18 years of age) will not be excluded during title/abstract screening, in case stratified data are reported in the full text.

b = This review seeks to identify the best available evidence. If there are not sufficient data on MPDs alone, studies of patients required to have a comorbid condition will be included.

c = Studies in which ginkgo biloba is evaluated together with another intervention will be eligible as long as these co-interventions are identical across treatment arms.

d = This list of outcomes is based on a preliminary search. Other types of efficacy outcomes identified during the search will be assessed during full-text screening to ascertain whether they are relevant to supporting the decision-making process.

e = The search strategy will not be restricted by language; this criterion will be applied during screening.

f = This review seeks to identify the best available evidence. If RCTs and comparative longitudinal observational studies do not provide sufficient evidence (i.e., <2 studies) to inform the ***Efficacy*** and ***Effectiveness*** HTA report chapters, respectively, the eligibility criteria will be expanded by descending the hierarchical evidence pyramid for study designs[105] to provide additional evidence. The detailed methodology of this review will be further outlined in the HTA report.

g = SLRs and meta-analyses will be included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses will be reviewed to identify additional publications not picked up by database searches.

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

## Table 5: Eligibility criteria: Clinical evidence for PAOD

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with PAOD, also known as PAD | • Patients without PAOD<br>• Studies in which not all patients have PAOD and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both PAOD and acute myocardial infarction)[b] |
| **Interventions** | Ginkgo biloba<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions, including herbal supplements or other formulations of ginkgo biloba[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Standard of care | Other comparators[c] |
| **Outcomes** | • Mobility<br>• Pain<br>• Peripheral blood circulation<br>• HRQoL<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f]<br>• Comparative longitudinal observational studies[f] | • Comparative cross-sectional studies[f]<br>• Single-arm clinical or observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, PAD = peripheral arterial disease, PAOD = peripheral arterial occlusive disease, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review

*Notes*

a = Studies in which only a subset of patients meets the relevant eligibility criteria (e.g. some do not have PAOD or are younger than 18 years of age) will not be excluded during title/abstract screening, in case stratified data are reported in the full text.

b = This review seeks to identify the best available evidence. If there are not sufficient data on PAOD alone, studies of patients required to have a comorbid condition will be included.

c = Studies in which ginkgo biloba is evaluated together with another intervention will be eligible as long as these co-interventions are identical across treatment arms.

d = This list of outcomes is based on a preliminary search. Other types of efficacy outcomes identified during the search will be assessed during full-text screening to ascertain whether they are relevant to supporting the decision-making process.

e = The search strategy will not be restricted by language; this criterion will be applied during screening.

f = This review seeks to identify the best available evidence. If RCTs and comparative longitudinal observational studies do not provide sufficient evidence (i.e., <2 studies) to inform the ***Efficacy*** and ***Effectiveness*** HTA report chapters, respectively, the

eligibility criteria will be expanded by descending the hierarchical evidence pyramid for study designs[105] to provide additional evidence. The detailed methodology of this review will be further outlined in the HTA report.

g = SLRs and meta-analyses will be included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses will be reviewed to identify additional publications not picked up by database searches.

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

## Table 6: Eligibility criteria: Clinical evidence for vertigo

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with vertigo/dizziness (peripheral or central vestibular system dysfunction). This includes acute vestibular syndrome (i.e. usually manifests with a single episode, such as vestibular neuritis), episodic vestibular syndrome (i.e. recurrent by nature, such as Ménière's disease or vestibular migraine), and chronic vestibular syndrome (i.e. persistent symptoms over an extended period of time, such as cerebellar degeneration). Studies of subtypes of vertigo are eligible. | • Patients without vertigo<br>• Studies in which not all patients have vertigo and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study of patients with vertigo and hypertension)[b] |
| **Interventions** | Ginkgo biloba<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions, including herbal supplements or other formulations of ginkgo biloba [c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Standard of care | Other comparators[c] |
| **Outcomes** | • Timing and intensity of vestibular symptoms, including patient-perceived handicap<br>• HRQoL<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f]<br>• Comparative longitudinal observational studies[f] | • Comparative cross-sectional studies[f]<br>• Single-arm clinical or observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review

*Notes*

a = Studies in which only a subset of patients meets the relevant eligibility criteria (e.g. some do not have vertigo or are younger than 18 years of age) will not be excluded during title/abstract screening, in case stratified data are reported in the full text.

b = This review seeks to identify the best available evidence. If there are not sufficient data on vertigo alone, studies of patients required to have a comorbid condition will be included.

c = Studies in which ginkgo biloba is evaluated together with another intervention will be eligible as long as these co-interventions are identical across treatment arms.

d = This list of outcomes is based on a preliminary search. Other types of efficacy outcomes identified during the search will be assessed during full-text screening to ascertain whether they are relevant to supporting the decision-making process.

e = The search strategy will not be restricted by language; this criterion will be applied during screening.

f = This review seeks to identify the best available evidence. If RCTs and comparative longitudinal observational studies do not provide sufficient evidence (i.e., <2 studies) to inform the ***Efficacy*** and ***Effectiveness*** HTA report chapters, respectively, the

eligibility criteria will be expanded by descending the hierarchical evidence pyramid for study designs[105] to provide additional evidence. The detailed methodology of this review will be further outlined in the HTA report.

g = SLRs and meta-analyses will be included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses will be reviewed to identify additional publications not picked up by database searches.

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

## Table 7: Eligibility criteria: Clinical evidence for tinnitus

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with tinnitus. This includes acute tinnitus (duration <3 months), chronic tinnitus (duration >3 months), and sub-acute tinnitus (although this term is rarely used, studies describing patients with sub-acute tinnitus will be included for completeness). Studies of subtypes of tinnitus are eligible. | • Patients without tinnitus<br>• Studies in which not all patients have tinnitus and data are not stratified<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study of patients with tinnitus and depression)[b] |
| **Interventions** | Ginkgo biloba<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions, including herbal supplements or other formulations of ginkgo biloba[b] |
| **Comparators** | • Placebo<br>• No treatment<br>• Standard of care | Other comparators[c] |
| **Outcomes** | • Tinnitus severity<br>• Tinnitus loudness<br>• Level of hearing loss<br>• HRQoL<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f]<br>• Comparative longitudinal observational studies[f] | • Comparative cross-sectional studies[f]<br>• Single-arm clinical or observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews<br><br>**Economic evidence:**<br>• Divergent study design |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review

*Notes*

a = Studies in which only a subset of patients meets the relevant eligibility criteria (e.g. some do not have tinnitus or are younger than 18 years of age) will not be excluded during title/abstract screening, in case stratified data are reported in the full text.

b = This review seeks to identify the best available evidence. If there are not sufficient data on tinnitus alone, studies of patients required to have a comorbid condition will be included.

c = Studies in which ginkgo biloba is evaluated together with another intervention will be eligible as long as these co-interventions are identical across treatment arms.

d = This list of outcomes is based on a preliminary search. Other types of efficacy outcomes identified during the search will be assessed during full-text screening to ascertain whether they are relevant to supporting the decision-making process.

e = The search strategy will not be restricted by language; this criterion will be applied during screening.

f = This review seeks to identify the best available evidence. If the RCTs and comparative longitudinal observational studies do not provide sufficient evidence (i.e., <2 studies) to inform the ***Efficacy*** and ***Effectiveness*** HTA report chapters, respectively, the eligibility criteria will be expanded by descending the hierarchical evidence pyramid for study designs[105] to provide additional evidence. The detailed methodology of this review will be further outlined in the HTA report.

g = SLRs and meta-analyses will be included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses will be reviewed to identify additional publications not picked up by database searches.

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

### 6.1.3 Data extraction, analysis, and quantitative synthesis

#### 6.1.3.1 Data extraction

Data will be extracted from included publications by one reviewer and complete confirmation of the data extracted will be conducted by a second reviewer. A third reviewer will be consulted if agreement is not reached between reviewers. Data extraction will be completed in a Microsoft Excel spreadsheet. Where multiple publications (including trial registration records) are available for the same trial, all publications will be utilised to complete data extraction.

A list of data elements to be extracted from each included publication is provided below. Please note that although the list below is comprehensive, additional items may be added if unanticipated data are available:

- **Trial information:** author, publication date, study identifier, study objective, source of funding, country, number of patients randomised, enrolment dates, randomisation technique, allocation concealment details, blinding, maximal follow-up duration, inclusion and exclusion criteria, statistical methods (i.e. methods for handling missing data, type of statistical test utilised), primary and secondary outcomes of interest as described by trial authors, patient attrition (per outcome where available)
- **Demographic information and baseline clinical characteristics (per treatment arm):** number of participants with available data, age, sex, BMI, definition of disease, concomitant medications, geography, and race/ethnicity
- **Intervention and comparator details:** dose, route, formulation, duration of intervention, and any co-interventions administered alongside the intervention and comparator(s)
- **Outcomes of interest:** measurement tool, time point of follow-up, and results for outcomes detailed in ***Section 4.4***
- **Others:** limitations of the study that do not fall clearly under standard quality assessment (e.g. the trial was stopped early, unexpected changes to prespecified trial methodology).

#### 6.1.3.2 Overall quality of evidence appraisal

The overall quality of evidence will be appraised using the GRADE approach. The 5 domains (imprecision, inconsistency, indirectness, risk of bias, and publication bias) of the GRADE framework will be scored (high, moderate, low, very low). The overall certainty of the evidence on the outcome level will be appraised by one researcher and will be fully reviewed by a second researcher. Differences will be resolved by discussion, and in case of discrepancy, a third researcher will be consulted to reach consensus. The overall certainty of the evidence will be summarised in a GRADE summary of findings table, using the GRADEpro GDT software (Evidence Prime Inc., Canada).

#### 6.1.3.3 Statistical analysis and synthesis methods

For each efficacy and safety outcome with sufficient reported data, studies with similar study design characteristics, intervention-comparator characteristics, and outcomes/endpoint characteristics will be included in the meta-analysis. A meta-analysis provides a method for integrating quantitative data from multiple studies. The advantages are that: (1) the results from individual studies are combined, improving the estimation of the overall effect size; (2) statistical power is increased; (3) confidence intervals (CIs) for the overall effect size can be calculated; and (4) factors related to heterogeneity in the results reported by individual studies can be investigated.

Should a meta-analysis be possible, a random-effects model will be utilised for the analysis. Dichotomous outcomes (e.g. AEs) will be reported using odds ratios (ORs)[C] with 95% CIs.[D] Continuous outcomes will be reported as mean difference (MD) and/or standardised mean difference (SMD) with 95% CIs, which will be used to account for differences in the measurement scales reported for outcomes across included studies. Meta-analysis results will be illustrated using forest plots, as they provide a visual representation of the reported effect sizes and uncertainty across the included studies. Heterogeneity will be assessed using both the $I^2$ statistic and the $\tau^2$ statistic. An $I^2$ of 0% to 40% is low heterogeneity (i.e. may not be important), 30% to 60% is moderate, 50% to 90% is substantial, and 75% to 100% is considerable heterogeneity.[103] Should sufficient data be available, subgroup analyses may be performed to examine differences in effect estimates depending on characteristics of the population, intervention and/or comparator. Based on the anticipated heterogeneity within each population of interest, underlying aetiology and disease subtype will be prioritised for subgroup analyses. In addition, subgroup analyses for dosage (120 mg vs. 240 mg) and formulation of ginkgo biloba will be considered. A detailed statistical plan will be completed once eligible studies have been identified and the availability of data has been assessed. A protocol amendment will be completed prior to any statistical testing. All statistical analyses will be conducted using R version 4.4.1.[106] In cases where a meta-analysis is not possible, ranges of effect estimates will be reported and narratively synthesised. The uncontrolled observational studies identified through published SLRs and monographs will be summarized narratively.

## 6.2 Systematic literature review of economic evidence

### 6.2.1 Databases and search strategy

The SLR of economic evidence will be conducted in accordance with guidance from the Cochrane Handbook for Systematic Reviews of Interventions[103] and the reporting will consider all items from the PRISMA checklist.[104] The search parameters for the identification of relevant literature are detailed in ***Table 8***. Because there is likely to be substantial overlap with the references identified in

[C] Statistical analyses will be conducted using log(OR) but reported as OR for interpretability.
[D] Note that should dichotomous events be rare (e.g. mortality), special statistical methods may be required for outcomes in which no events occurred. The specific statistical methodology will depend on the characteristics of the identified studies (e.g. studies in which both treatment arms had zero events may be excluded from the meta-analysis).

the SLR of clinical evidence, a single, combined search strategy for each database will be utilised (***Appendix A***).

**Table 8: Search parameters**

| | |
|---|---|
| **Electronic databases** | MEDLINE, Embase, EconLit, CENTRAL CDSR, and NHS EED (all via OvidSP); INAHTA |
| **Other sources** | Reference lists of relevant published SLRs/meta-analyses identified in the database search |
| **Publication type** | Journal articles only |
| **Search dates** | No restriction |
| **Language** | No restriction[a] |
| **Geography** | No restriction |

*Abbreviations*

CDSR = Cochrane Database of Systematic Reviews, EED = Economic Evaluation Database, INAHTA – International Network of Agencies for Health Technology Assessment, NHS = National Health Service, SLR = systematic literature review

*Notes*

a = Although the search strategy will not be restricted by language, publications in languages other than English, German, Italian, and French will be excluded during title/abstract screening.

### 6.2.2 Study selection

The electronic records of the articles retrieved by the database searches will be exported into an EndNote library (Clarivate Analytics, USA), and after deduplication, they will be imported into DistillerSR for study selection. Screening will be performed to include studies that meet the pre-defined study selection criteria (***Table 8***), as well as to provide an exclusion reason for each publication/study that does not meet at least one of the pre-defined criteria. Screening will be conducted in 2 levels: first, the title and abstract of each publication will be assessed for relevancy to the objectives of the SLR; and second, articles that seem to contain relevant data will undergo full-text screening.

The identified title/abstracts and full-text publications will be screened by 2 independent reviewers, and conflicts will be resolved via discussion. If a consensus cannot be reached, a third reviewer will be consulted. SLRs/meta-analyses of relevant populations identified via the database search will be flagged during the screening process and utilised to identify any additional studies. The studies included in such SLRs/meta-analyses will be compared with the final list of included studies in this SLR to determine if any additional studies are eligible.

**Table 9: Eligibility criteria for economic evidence**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Interventions** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Comparators** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Outcomes** | • All-cause healthcare costs<br>• Disease-related healthcare costs<br>• ICERs<br>• Incremental and total costs<br>• Incremental and total effects, including QALYs and LYs | Other outcomes |
| **Language** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • Cost-effectiveness analyses<br>• BIMs<br>• Cost analyses<br>• Cost-utility analyses<br>• Cost-consequence analyses<br>• Cost-minimisation analyses<br>• Cost-benefit analyses | • SLRs |

*Abbreviations*

BIM = budget impact model, ICER = incremental cost-effectiveness ratio, LY = life-year, QALY = quality-adjusted life-year, SLR = systematic literature review

### 6.2.3 Data extraction, quality assessment, and synthesis

#### 6.2.3.1 Data extraction

Data will be extracted from included publications by one reviewer and complete confirmation of the data extracted will be conducted by a second reviewer. A third reviewer will be consulted if agreement is not reached between reviewers. Data extraction will be completed in a Microsoft Excel spreadsheet.

A list of data elements to be extracted from each included publication is provided below. Please note that although the list below is comprehensive, additional items may be added if unanticipated data are available:

- **Study information:** author, publication date, study identifier, study objective, source of funding, country, type of economic evaluation, model structure, key assumptions, source(s) of model inputs, discount rate, perspective, and time horizon
- **Population characteristics:** definition of disease, number of participants with available data, age, sex, BMI, concomitant medications, geography, and race/ethnicity

- **Intervention and comparator details:** dose, route, formulation, duration of intervention, and any co-interventions administered alongside the intervention and comparator(s)
- **Outcomes of interest:** measurement methods, time point of follow-up, and results for economic outcomes detailed in ***Section 4.4***, as well as the results of any sensitivity analyses

6.2.3.2 Quality assessment

The reporting quality of health economic evaluations will be assessed using the CHEERS statement.[107] The reporting quality of each health economic evaluation will be assessed by one researcher and fully reviewed by a second researcher. Differences will be resolved by discussion, and in case of discrepancy a third researcher will be consulted to reach consensus.

6.2.3.3 Synthesis

Evidence from available health economic evaluations will be synthesised narratively and tabular summaries will be provided. Study characteristics and outcomes will be grouped by patient population, sub-population (e.g. underlying pathology of vertigo), study type, and geography. Economic outcomes will also be used to provide information for the BIM described in ***Section 6.3***.

## 6.3 BIM

### 6.3.1 Model conceptualisation

The initial step in developing an economic model will be to assess potential inputs, key assumptions, and data sources by developing a conceptual framework. The specific objectives of the model conceptualisation phase are outlined below:

- Outputs from the SLR will be leveraged in the development of the models as available; however, when needed, targeted literature searches will be conducted to supplement gaps in data needed to inform the models.
    - As the intent of a supplemental targeted literature search is to support model development, the searches will be performed ad hoc; separate steps and deliverables that would typically be associated with a systematic search, such as search string/strategy, PRISMA diagram, list of excluded articles, or report, will not be developed.
- Ensure the BIM is developed in accordance with appropriate guidelines (e.g. National Institute for Health and Care Excellence [NICE] and International Society for Pharmacoeconomics and Outcomes Research [ISPOR] Model Guidelines) and aligned with the latest FOPH requirements.

***Table 10*** presents an overview of the BIM.

**Table 10: BIM overview**

| | |
|---|---|
| **Perspective** | Swiss Healthcare Payers' |
| **Time horizon** | 1 to 5 years (user-selectable) |
| **Population** | Adults with MPDs, PAOD, vertigo, or tinnitus, as described in **Section 4.1** |
| **Comparators** | Standard of care |
| **Costs** | • Drug costs<br>• Medical costs as deemed appropriate/relevant (e.g. monitoring, AEs) |
| **Currency** | 2024 Swiss Franc (CHF) |
| **Budget impact** | • Total costs<br>• Total budget impact<br>• Budget impact will be reported in graphical and tabular formats |
| **Sensitivity analysis** | One-way sensitivity analysis. This feature allows users to set a low and high value for key model inputs and then, at a click of a button, assess the impact on the model output. The results are presented in the form of a tornado diagram. |

*Abbreviations*

AE = adverse event, MPD = mental performance deficit, PAOD = peripheral arterial occlusive disease

### 6.3.2 Model development

Based upon the model specifications finalised during the model conceptualisation phase, development of the model will commence as described below.

- Model structure: The first structural draft of the BIM will be developed in Excel, showing the layout and calculations within the model to capture the target population, comparators, and costs. At this point in the development process, many model values may be placeholder values until the model structure is finalised.
- Model with inputs populated: The model inputs will be populated based on the data sources identified during the model conceptualisation phase.
- Functional model: The final model will include default values, navigation functionality, and other functionality as described above.

The model will be developed in current Microsoft Excel software to ensure maximum functionality and ease of distribution.

### 6.3.3 Model finalization

The overview of the model validation process is depicted in ***Figure 1***. During the development process, the model will undergo unit and integration testing by the model developer to verify correct calculations. During the model enhancement process, navigation, controls, and data validation are incorporated, and the model is further tested to confirm full functionality and that the model is

detailed to provide a professional appearance. Finally, the model is independently tested for validity, accuracy, functionality, and appearance by an independent reviewer.

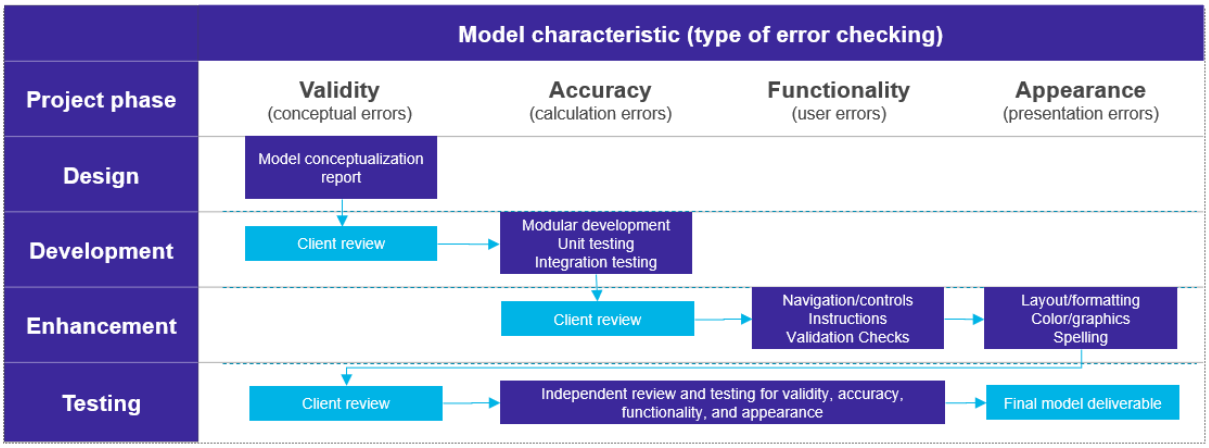


**Figure 1: Model testing and validation process**

## 6.4 Targeted literature review of ethical, legal, social and organisational issues

### 6.4.1 Databases and search strategy

To address the ELSO issues, all publications included in the SLRs described above will be reviewed for any relevant information. Subsequently, a targeted literature search in Embase and MEDLINE (see ***Appendix B*** for the detailed search strategy) will be conducted to supplement the findings.

### 6.4.2 Study selection

Inclusion and exclusion criteria are presented in ***Table 11*** and were developed in accordance with those of the clinical and economic evidence search (see ***Table 4***, ***Table 5***, ***Table 6***, ***Table 7,*** and ***Table 9***). However, there will be no restrictions on study design, as discussions on ELSO outcomes will likely encompass a range of study methodologies. A single researcher will screen and review the literature to identify studies pertinent to ELSO domains.

**Table 11: Eligibility criteria for ELSO issues**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Interventions** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Comparators** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Outcomes** | Discussion of ethical, legal, social, or organisational aspects | No discussion of ethical, legal, social, or organisational aspects |
| **Language** | As for **Table 4, Table 5, Table 6,** and **Table 7** | |
| **Time horizon** | 2015 to present | |
| **Study design/ publication type** | Journal articles<br>No restrictions on study design | Conference abstracts |

### 6.4.3 Data extraction and synthesis

It is important to note that a formal data extraction and an assessment of the quality of evidence for ELSO outcomes will not be conducted. The primary ELSO aspects identified through this targeted search will be presented descriptively, as this review will not follow a systematic methodology. This approach is deemed appropriate as the main goal is to highlight key aspects relevant to ELSO but not to provide an exhaustive or systematic review of the literature on these domains.

# 7. Summary and outlook

## 7.1 Summary

The HTA report following this HTA protocol will present the best available evidence on the use of ginkgo biloba as a standalone therapy or as adjunctive treatment for MPDs, PAOD, vertigo and tinnitus. This evidence will serve to support the FOPH during the re-evaluation of ginkgo biloba and inform reimbursement policy moving forward.

There are several potential challenges that may arise during this HTA review:

- MPDs can have varying aetiologies and are described in many different terms in the literature. To combat this challenge, the search strategy will not include condition-specific keywords but will instead focus on intervention and study design terms. During screening and data extraction, information about the populations will be collected so that similar populations can be grouped appropriately for synthesis.
- It is possible that some important outcomes may not be fully represented in comparative studies. Findings from uncontrolled observational studies, identified through SLRs and monographs, will be summarised and incorporated into the discussion and the assessment of the ELSO aspects.
- Gingko biloba can be given in combination with pharmacotherapy for the conditions of interest, so it may be difficult to determine the additional treatment effects attributable to ginkgo biloba. Since there are a wide variety of oral preparations of ginkgo, with flavonoids, terpenoids, and organic acids as the main active ingredient, and an option with injectable administration, there is heterogeneity in the dose and exposure to ginkgo biloba. The data will be collected as reported and will be synthesised, with appropriate caveats regarding heterogeneity included as needed. In addition, studies of co-interventions will only be eligible if they are received by all treatment groups.
- There may be difficulties in determining the budget impact by indication, given ginkgo biloba's status as an herbal medicinal product. Rather, the BIM will capture the total budget impact across indications, based on utilisation and sales data.

## 7.2 Outlook

The HTA protocol is followed by the production of an HTA report. The objective of the HTA report is to generate a focused assessment of various aspects of the health technology in question. The applied analytic methods, their execution and the results are described. The analytical process is comparative, systematic, and transparent. The external review group that was consulted during the protocol phase is consulted again during the HTA phase. Subsequently, the HTA draft report is presented to the stakeholders for consultation. Communication with the reviewers and the stakeholders is coordinated by the FOPH.

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# 9. Appendices

# A. Search strategies for clinical and economic evidence

### Table 12: Search strategy for Embase (via OvidSP)

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | Ginkgo biloba extract/ |
| | 3 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 4 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 5 | ((drug-extract ratio or DER or DEV) adj1 35-67).tw. |
| | 6 | or/1-5 |
| Observational studies | 7 | Clinical study/ |
| | 8 | Case control study/ |
| | 9 | Family study/ |
| | 10 | Longitudinal study/ |
| | 11 | Retrospective study/ |
| | 12 | Prospective study/ |
| | 13 | Randomized controlled trials/ |
| | 14 | 12 not 13 |
| | 15 | Cohort analysis/ |
| | 16 | (Cohort adj (study or studies)).mp. |
| | 17 | (Case control adj (study or studies)).tw. |
| | 18 | (follow up adj (study or studies)).tw. |
| | 19 | (observational adj (study or studies)).tw. |
| | 20 | (epidemiologic$ adj (study or studies)).tw. |
| | 21 | (cross sectional adj (study or studies)).tw. |
| | 22 | or/7-11,14-21 |
| RCTs | 23 | Clinical Trial/ |
| | 24 | Randomized Controlled Trial/ |
| | 25 | controlled clinical trial/ |
| | 26 | multicenter study/ |
| | 27 | Phase 3 clinical trial/ |
| | 28 | Phase 4 clinical trial/ |
| | 29 | exp RANDOMIZATION/ |
| | 30 | Single Blind Procedure/ |
| | 31 | Double Blind Procedure/ |
| | 32 | Crossover Procedure/ |
| | 33 | PLACEBO/ |
| | 34 | randomi?ed controlled trial$.tw. |
| | 35 | rct.tw. |
| | 36 | (random$ adj2 allocat$).tw. |
| | 37 | single blind$.tw. |
| | 38 | double blind$.tw. |
| | 39 | ((treble or triple) adj blind$).tw. |
| | 40 | placebo$.tw. |
| | 41 | Prospective Study/ |
| | 42 | or/23-41 |
| Economic/cost outcomes | 43 | Economics/ |
| | 44 | Cost analysis/ |
| | 45 | Cost allocation/ |
| | 46 | Cost control/ |
| | 47 | Cost savings/ |

| Search facet | # | Search strings |
|---|---|---|
| | 48 | Cost of illness/ |
| | 49 | Health care costs/ |
| | 50 | Direct service costs/ |
| | 51 | Drug costs/ |
| | 52 | Hospital costs/ |
| | 53 | Health expenditures/ |
| | 54 | Capital expenditures/ |
| | 55 | Economics, hospital/ |
| | 56 | Economics, medical/ |
| | 57 | Economics, nursing/ |
| | 58 | Economics, pharmaceutical/ |
| | 59 | ((health?care or unit) adj cost$).mp. |
| | 60 | (fiscal or funding or financial or finance).tw. |
| | 61 | (cost adj (estimate$ or variable$)).mp. |
| | 62 | (economic$ or pharmacoeconomic$ or price$ or pricing or fiscal or financial or finance or funding).tw. |
| | 63 | Socioeconomics/ |
| | 64 | Economic aspect/ |
| | 65 | Financial management/ |
| | 66 | Health care cost/ |
| | 67 | Health care financing/ |
| | 68 | Health economics/ |
| | 69 | Hospital cost/ |
| | 70 | resource allocation/ |
| | 71 | resource management/ |
| | 72 | (health care utili?ation or hospitali?ation$ or resource utili?ation or resource$ or cost$).mp. |
| | 73 | health care utilization/ |
| | 74 | hospitalization/ |
| | 75 | Cost/ |
| | 76 | exp Health Economics/ |
| | 77 | Budget/ |
| | 78 | budget*.ti,ab,kf. |
| | 79 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. |
| | 80 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 |
| | 81 | (value adj2 (money or monetary)).mp. |
| | 82 | or/43-81 |
| Economic evaluations | 83 | economic evaluation*.ti,ab,kf. or economic evaluation/ |
| | 84 | ((cost* or economic) adj2 (effective* or assess* or utilit* or benefit* or minimi* or analy* or outcome or outcomes or model)).ab,kf. |
| | 85 | (value adj2 (money or monetary)).ti,ab,kf. |
| | 86 | statistical model/ |
| | 87 | exp economic model/ |
| | 88 | probability/ |
| | 89 | economic model*.ab,kf. |
| | 90 | markov.ti,ab,kf. |
| | 91 | monte carlo method/ |
| | 92 | monte carlo.ti,ab,kf. |
| | 93 | decision theory/ |
| | 94 | decision tree/ |
| | 95 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. |
| | 96 | Quality-Adjusted Life Year/ |

| Search facet | # | Search strings |
|---|---|---|
| | 97 | quality adjusted life.ti,ab,kf. |
| | 98 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. |
| | 99 | disability adjusted life year*.ti,ab,kf. |
| | 100 | disability-adjusted life year/ |
| | 101 | (daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf. |
| | 102 | healthy life expectancy/ |
| | 103 | cost benefit analysis/ or "cost effectiveness analysis"/ or "cost utility analysis"/ |
| | 104 | (cost effectiveness or cost-effectiveness).ti,ab,kf. |
| | 105 | (cost benefit or cost-benefit).ti,ab,kf. |
| | 106 | (cost utility or cost-utility).ti,ab,kf. |
| | 107 | (incremental* adj2 cost*).tw. |
| | 108 | ICER.tw. |
| | 109 | utilities.tw. |
| | 110 | or/83-109 |
| Combine all relevant outcomes/study designs | 111 | 22 or 42 or 82 or 110 |
| Combine with intervention terms | 112 | 6 and 111 |
| Exclude animal studies and ineligible publication types | 113 | exp animal/ not exp human/ |
| | 114 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 115 | letter/ or editorial/ or note/ or case report/ |
| | 116 | (letter or editorial or note or case reports).pt. |
| | 117 | anonymous.au. |
| | 118 | or/113-117 |
| | 119 | 112 not 118 |
| | 120 | review.pt. not (systematic adj2 review).pt,ti,ab. |
| | 121 | 119 not 120 |
| Exclude conference abstracts | 122 | conference$.pt,st. |
| | 123 | 121 not 122 |

## Table 13: Search strategy for MEDLINE (via OvidSP)

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 4 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 5 | or/1-4 |
| Observational studies | 6 | Epidemiologic studies/ |
| | 7 | exp case control studies/ |
| | 8 | exp cohort studies/ |
| | 9 | Case control.tw. |
| | 10 | (cohort adj (study or studies)).tw. |
| | 11 | Cohort analy$.tw. |
| | 12 | (Follow up adj (study or studies)).tw. |
| | 13 | (observational adj (study or studies)).tw. |
| | 14 | Longitudinal.tw. |
| | 15 | Retrospective.tw. |
| | 16 | Cross sectional.tw. |
| | 17 | Cross-sectional studies/ |
| | 18 | or/6-17 |
| RCTs | 19 | Randomized Controlled Trials as Topic/ |
| | 20 | randomized controlled trial/ |
| | 21 | Random Allocation/ |
| | 22 | Double Blind Method/ |
| | 23 | Single Blind Method/ |

| Search facet | # | Search strings |
|---|---|---|
| | 24 | clinical trial/ |
| | 25 | clinical trial, phase i.pt. |
| | 26 | clinical trial, phase ii.pt. |
| | 27 | clinical trial, phase iii.pt. |
| | 28 | clinical trial, phase iv.pt. |
| | 29 | controlled clinical trial.pt. |
| | 30 | randomized controlled trial.pt. |
| | 31 | multicenter study.pt. |
| | 32 | clinical trial.pt. |
| | 33 | exp Clinical Trials as topic/ |
| | 34 | (clinical adj trial$).tw. |
| | 35 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. |
| | 36 | PLACEBOS/ |
| | 37 | placebo$.tw. |
| | 38 | randomly allocated.tw. |
| | 39 | (allocated adj2 random$).tw. |
| | 40 | or/19-39 |
| Economic/cost outcomes | 41 | Economics/ |
| | 42 | Cost analysis/ |
| | 43 | Cost allocation/ |
| | 44 | Cost control/ |
| | 45 | Cost savings/ |
| | 46 | Cost of illness/ |
| | 47 | Health care costs/ |
| | 48 | Direct service costs/ |
| | 49 | Drug costs/ |
| | 50 | Hospital costs/ |
| | 51 | Health expenditures/ |
| | 52 | Capital expenditures/ |
| | 53 | Economics, hospital/ |
| | 54 | Economics, medical/ |
| | 55 | Economics, nursing/ |
| | 56 | Economics, pharmaceutical/ |
| | 57 | ((health?care or unit) adj cost$).mp. |
| | 58 | (fiscal or funding or financial or finance).tw. |
| | 59 | (cost adj (estimate$ or variable$)).mp. |
| | 60 | (economic$ or pharmacoeconomic$ or price$ or pricing or fiscal or financial or finance or funding).tw. |
| | 61 | Socioeconomic Factors/ |
| | 62 | Economic Status/ |
| | 63 | Financial management/ |
| | 64 | Health care cost/ |
| | 65 | Health economics/ |
| | 66 | Hospital cost/ |
| | 67 | resource allocation/ |
| | 68 | (health care utili?ation or hospitali?ation$ or resource utili?ation or resource$ or cost$).mp. |
| | 69 | health care utilization/ |
| | 70 | hospitalization/ |
| | 71 | Cost/ |
| | 72 | exp Health Economics/ |
| | 73 | Budget/ |
| | 74 | budget*.ti,ab,kf. |
| | 75 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. |
| | 76 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 |
| | 77 | (value adj2 (money or monetary)).mp. |

| Search facet | # | Search strings |
|---|---|---|
| | 78 | or/41-77 |
| Health economic models | 79 | ((cost* or economic) adj2 (effective* or assess* or utilit* or benefit* or minimi* or analy* or outcome or outcomes or model)).ab,kf. |
| | 80 | (value adj2 (money or monetary)).ti,ab,kf. |
| | 81 | exp models, economic/ |
| | 82 | economic model*.ab,kf. |
| | 83 | markov chains/ |
| | 84 | markov.ti,ab,kf. |
| | 85 | monte carlo method/ |
| | 86 | monte carlo.ti,ab,kf. |
| | 87 | exp Decision Theory/ |
| | 88 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. |
| | 89 | (cost effectiveness or cost-effectiveness).ti,ab,kf. |
| | 90 | (cost benefit or cost-benefit).ti,ab,kf. |
| | 91 | (cost utility or cost-utility).ti,ab,kf. |
| | 92 | (incremental* adj2 cost*).tw. |
| | 93 | ICER.tw. |
| | 94 | utilities.tw. |
| | 95 | Quality-Adjusted Life Years/ |
| | 96 | quality adjusted life.ti,ab,kf. |
| | 97 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. |
| | 98 | disability adjusted life year*.ti,ab,kf. |
| | 99 | disability-adjusted life years/ |
| | 100 | (daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf. |
| | 101 | healthy life expectancy/ |
| | 102 | Cost-Effectiveness Analysis/ or Cost-Benefit Analysis/ |
| | 103 | or/79-102 |
| Combine all relevant outcomes/study designs | 104 | 18 or 40 or 78 or 103 |
| Combine with intervention terms | 105 | 5 and 104 |
| Exclude animal studies and ineligible publication types | 106 | exp animal/ not exp human/ |
| | 107 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 108 | letter/ or editorial/ or note/ or case report/ |
| | 109 | (letter or editorial or note or case reports).pt. |
| | 110 | anonymous.au. |
| | 111 | or/106-110 |
| | 112 | 105 not 111 |
| | 113 | review.pt. not (systematic adj2 review).pt,ti,ab. |
| | 114 | 112 not 113 |

**Table 14: Search strategy for Cochrane Central Register of Controlled Trials (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 4 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 5 | or/1-4 |
| Exclude animal studies and ineligible publication types | 6 | exp animals/ not exp humans/ |
| | 7 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 8 | (letter or editorial or comment$ or note or study guide or protocol).pt. |
| | 9 | case study/ or letter/ or editorial/ or case report/ or news/ or note/ or study guide/ |
| | 10 | anonymous.au. |
| | 11 | or/6-10 |
| | 12 | 5 not 11 |
| Exclude conference | 13 | (conference$ or Trial registry record).pt,st. |

| Search facet | # | Search strings |
|---|---|---|
| abstracts | 14 | 12 not 13 |

## Table 15: Search strategy for Cochrane Database of Systematic Reviews (via OvidSP)

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |
| Exclude ineligible publication types | 5 | (letter or editorial or comment$ or note or study guide or protocol).pt. |
| | 6 | 4 not 5 |

## Table 16: Search strategy for EconLit (via OvidSP)

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |

## Table 17: Search strategy for NHS Economic Evaluation Database (via OvidSP)

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |

## Table 18: Search strategy for European Union Clinical Trials Register

| Search facet | Search strings |
|---|---|
| Intervention | Ginkgo OR Gingko OR Ginko OR Maidenhair OR "Egb 761" OR Egb761 OR EGb-761 OR tebokan OR rezirkane OR symfona |

## Table 19: Search strategy for ClinicalTrials.gov

| Search facet | Search strings |
|---|---|
| Intervention | Ginkgo |
| | Gingko |
| | Ginko |
| | Maidenhair |
| | rezirkane |
| | symfona |
| | tebokan |
| | Egb 761 |
| | Egb761 |
| | EGb-761 |

*Notes:*

ClinicalTrials.gov does not allow for more complex searching syntax, so each item listed in this table will be searched individually in the “Intervention/treatment” category and all results will be reviewed for each search.

**Table 20: Search strategy for International Network of Agencies for Health Technology Assessment database**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ [MeSH search] |
| | 2 | (Ginkgo* or Gingko* or Ginko* or Maidenhair) [All] |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761). [All] |
| | 4 | or/1-3 |

# B. Search strategy for ELSO issues

**Table 21: Search strategy for ELSO issues**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | Ginkgo biloba extract/ |
| | 3 | (Ginkgo* or Gingko* or Ginko* or Maidenhair).tw. |
| | 4 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 5 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 6 | or/1-5 |
| Ethical, social, and legal items | 7 | exp Ethics, Clinical/ |
| | 8 | exp Ethical Analysis/ |
| | 9 | Legislation, Drug/ |
| | 10 | Social Change/ |
| | 11 | medical ethics/ |
| | 12 | drug legislation/ |
| | 13 | "social aspects and related phenomena"/ |
| | 14 | social aspect/ |
| | 15 | Social Responsibility/ |
| | 16 | Social Welfare/ |
| | 17 | Social Factors/ |
| | 18 | exp social structure/ |
| | 19 | (ethics or legal or law or social).ti,ab. |
| | 20 | or/7-19 |
| Organizational items | 21 | "Organisation and Administration"/ |
| | 22 | exp Health Facility Administration/ |
| | 23 | Policy/ |
| | 24 | Policy Making/ |
| | 25 | Organizational Policy/ |
| | 26 | Insurance, Health/ |
| | 27 | exp Insurance Coverage/ |
| | 28 | exp Drug Approval/ |
| | 29 | exp Health Services Accessibility/ |
| | 30 | health care organization/ |
| | 31 | exp health care system/ |
| | 32 | exp hospital organization/ |
| | 33 | exp health insurance/ |
| | 34 | (organization or organisation or policy or approval or coverage or reimburse* or access or disinvestment or drug dispensing or ((regulation or regulatory) adj3 (agency or agencies or medicine* or medication* or drug* or approval*))).ti,ab. |
| | 35 | or/21-34 |
| Combine terms | 36 | 6 and 20 |
| | 37 | 6 and 35 |
| | 38 | 36 or 37 |
| Exclude conference abstracts | 39 | conference$.pt,st. |
| | 40 | 38 not 39 |
| Remove duplicates | 41 | remove duplicates from 40 |

| Search facet | # | Search strings |
|---|---|---|
| Limit to last 10 years | 42 | limit 41 to yr="2015 -Current" |