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Health Technology Assessment (HTA)

HTA Report

Betahistine or cinnarizine with or without dimenhydrinate for Ménière's disease/syndrome and symptoms of vestibular vertigo and/or tinnitus

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Authors report no conflict of interest in relation to this project.

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Executive Summary

BACKGROUND

Ménière's disease is a disorder of the inner ear that can cause various symptoms. Patients with Ménière's disease experience episodes of vertigo, tinnitus, hearing loss and aural fullness. Vertigo refers to the feeling of motion when there is none or the feeling of distorted self-motion during a normal head movement and includes spinning vertigo and non-spinning vertigo. Patients with tinnitus experience a constant or intermittent ringing or other noise in the ear or in the head. Aural fullness is a sensation of pressure deep inside the ear. In Switzerland, betahistine and cinnarizine are reimbursed for patients experiencing symptoms of vertigo, tinnitus and hearing loss caused by Ménière's disease or other disorders. Furthermore, cinnarizine with dimenhydrinate is reimbursed for the symptomatic treatment of transient vertigo. The evidence for the coverage of these drugs is to be re-evaluated in the context of the Federal Office of Public Health (FOPH) health technology assessment (HTA) program. The presented evidence is intended to inform policy makers in their decision whether these drugs should continue to be reimbursed by the Swiss compulsory health insurance.

OBJECTIVE

This HTA report assesses the efficacy, effectiveness, safety, cost-effectiveness and budget impact, as well as ethical, legal, social, and organisational benefits and harms of betahistine and cinnarizine with or without dimenhydrinate for the treatment of vertigo, tinnitus and/or hearing loss caused by Ménière's disease or for the treatment of vertigo or tinnitus caused by other peripheral or central vestibular disorders.

METHODS

For the clinical systematic review a primary systematic literature search was conducted in PubMed (MEDLINE), Embase.com and the Cochrane Library to select randomised controlled trials (RCTs) on betahistine or cinnarizine with or without dimenhydrinate for vertigo, tinnitus and hearing loss caused by Ménière's disease or for vertigo and tinnitus caused by other peripheral or central vestibular disorders. Based on the output of the primary systematic literature search and expert opinion an additional systematic literature search was performed for RCTs on the most common indications that fall within the scope of the licensed indications for betahistine and cinnarizine with or without dimenhydrinate, i.e. vestibular migraine, vertebrobasilar insufficiency (VBI), transient ischemic attack (TIA), anterior inferior cerebellar artery (AICA) infarct, labyrinthine artery infarct and benign paroxysmal positional vertigo (BPPV). No additional search for comparative non-randomised studies was implemented. Studies were selected by applying pre-specified eligibility criteria during the selection process. Included RCTs were critically appraised with the revised Cochrane Risk of Bias

tool for randomised trials (RoB 2) and the extracted data was summarised narratively. When event rates and sample sizes were reported, risk ratios and 95% confidence intervals were calculated. Results reported on outcomes with relevant data missing for valid data interpretation were not included in the data synthesis. The overall certainty of the evidence on outcome level was assessed with GRADE.

The economic systematic review followed a procedure similar to the clinical systematic review. The searches were conducted in PubMed (MEDINE), Embase.com, Cochrane Library, as well as the economic databases Tufts Medical Centre Cost-Effectiveness Analysis (CEA) and the international HTA database. A cost-effectiveness model was built to estimate the cost-effectiveness of cinnarizine with dimenhydrinate for the treatment of vertigo caused by other disorders than Ménière's disease. A decision tree was modelled with a time horizon of 28 days. Due to lack of utility data, outcomes were expressed as cost per one point reduction on the mean vertigo score. A Swiss healthcare payer perspective was used. Based on the findings of the clinical systematic review, no cost-effectiveness models were built for betahistine or cinnarizine without dimenhydrinate for the treatment of Ménière's disease, vertigo or tinnitus. A budget impact analysis was run for betahistine, cinnarizine without dimenhydrinate, and cinnarizine with dimenhydrinate, using information from SASIS on volume and the Spezialitätenliste on prices of these treatments. For cinnarizine with dimenhydrinate, costs from the cost-effectiveness model were used to complement the budget impact model.

Ethical, legal, social and organisational (ELSO) issues were searched through the systematic literature searches and pragmatic searches and described narratively.

RESULTS

In the clinical systematic review 10 RCTs were included on licensed drug use and stratified in 4 groups: betahistine for Ménière's disease (4 RCTs), betahistine for vertigo (3 RCTs), cinnarizine for tinnitus (1 RCT), and cinnarizine with dimenhydrinate for vertigo (2 RCTs). Some of these RCTs missed relevant outcome data for valid data interpretation; these results are presented in an appendix to provide full insight in published RCT evidence.

In adult patients with Ménière's disease treated for 9 months with betahistine versus placebo no statistically significant differences were found in vertigo attack frequency (adjusted rate ratio 1.04 [95% CI 0.94 to 1.14]; 1 RCT; moderate certainty evidence) and tinnitus intensity (adjusted mean difference [aMD] +1.40 dB [95% confidence interval [CI] -5.10 to 7.90]; 1 RCT; low certainty evidence). Also, no statistically significant difference in hearing loss assessed at 4 different frequencies was found (range across frequencies evaluated aMD from +0.33 dB [95% CI -3.13 to 3.79] at 250 Hz to +2.83 dB [95% CI -1.93 to 7.59] at 1000 Hz; 1 RCT; low certainty evidence). No statistically significant differences were reported for 9-months betahistine versus placebo treatment for disease-specific health-related quality of life (HRQoL) assessed with the dizziness handicap

inventory (aMD +0.08 [95% CI -0.17 to 0.33]; mean total score range 0 [best]–4 [worst]; 1 RCT; moderate certainty evidence), vestibular disorders activities of daily living questionnaire (aMD -0.05 [95% CI -0.32 to 0.22]; score range 1 [best]–10 [worst]; 1 RCT; moderate certainty evidence), and mini-tinnitus impairment questionnaire (aMD -0.007 [95% CI -0.14 to 0.13]; score range 0 [best]–24 [worst]; 1 RCT; moderate certainty evidence). A statistically significant improvement in disease-specific HRQoL assessed with the dizziness handicap inventory was reported for 1-month betahistine treatment compared to no treatment (MD -6.1 [95% CI not reported]; score range 0 [best]–100 [worst]; 1 RCT; very low certainty evidence). There was no statistically significant difference in the occurrence of serious adverse events for betahistine versus placebo in patients with Ménière's disease up to 9 months of treatment (risk ratio [RR] 1.12 (95% CI 0.53 to 2.38); 2 RCTs; low certainty evidence).

In adult patients with diverse vertigo aetiologies treated up to 3 months with betahistine versus placebo the results for 3 different vertigo outcomes were lacking and seem not consistent. Compared to baseline, betahistine treatment resulted in a statistically significant decrease in vertigo attack frequency (effect size [95% CI] not reported; 1 RCT; very low certainty evidence) and vertigo attack severity (effect size [95% CI] not reported; 2 RCTs; very low certainty evidence) versus a statistically significant decrease for placebo treatment in vertigo attack duration (effect size [95% CI] not reported; 1 RCT; very low certainty evidence). No statistically significant difference was found in investigator-reported vertigo symptoms for betahistine versus placebo (RR 0.88 [95% CI 0.45 to 1.69]; 1 RCT; very low certainty evidence). No data was reported on HRQoL. No serious adverse events were encountered in the treatment with betahistine or placebo (RR not estimable; 3 RCTs; very low certainty evidence).

In adult patients with idiopathic subjective tinnitus treated for 10 weeks with cinnarizine versus placebo no statistically significant differences were found in tinnitus disturbance during activity or rest ($MD_{activity}$ -0.1 [95% CI not reported]; MD_{rest} -0.15 [95% CI not reported]; score range 0 [best]–4 [worst]; 1 RCT; very low certainty evidence) nor in patient-reported tinnitus symptoms (RR 2.00 [95% CI 0.14 to 28.76]; 1 RCT; very low certainty evidence). No data was reported on HRQoL or serious adverse events.

In adult patients with diverse vertigo aetiologies treated for 4 weeks with cinnarizine with dimenhydrinate the vertigo symptoms statistically significantly improved compared to placebo, assessed with the mean vertigo score (aMD -1.3 [95% CI not reported]; score range 0 [best]–3 [worst]; and aMD -0.56 [95% CI -0.38 to -0.75]; score range 0 [best]–4 [worst]; 2 RCTs; moderate certainty evidence). A statistically non-significant improvement of patient and investigator-reported vertigo symptoms was reported (RR 3.44 [95% CI 0.38 to 31.02]; 2 RCTs; very low certainty evidence). No data was reported on HRQoL. No serious adverse events were encountered in the treatment with cinnarizine with dimenhydrinate or placebo (RR not estimable; 2 RCTs; low certainty evidence).

In the economic review. no economic evaluations were included. Only for vertigo caused by other vestibular disorders than Ménière's disease treated with cinnarizine with dimenhydrinate a positive treatment was found compared to placebo in the clinical review. Evidence for a positive treatment effect was lacking for cinnarizine for Ménière's disease and tinnitus while for betahistine and cinnarizine without dimenhydrinate the evidence was lacking for any of the conditions of interest. Therefore, a cost-effectiveness model was only developed for patients with vestibular vertigo not caused by Ménière's disease treated with cinnarizine with dimenhydrinate. The cost-effectiveness model for the treatment of vertigo caused by other disorders than Ménière's disease showed that treatment with cinnarizine with dimenhydrinate was dominant (i.e. lower costs and more effective) compared to no treatment. Scenario analyses and sensitivity analyses showed the robustness of the results. The estimated budget impact of betahistine was CHF 17.2 million over a 5-year period. For cinnarizine without dimenhydrinate, the estimated budget impact was CHF 0.8 million over a 5-year period. The use of cinnarizine with dimenhydrinate resulted in projected cumulative budget savings of CHF 1.2 million over a 5-year period. Note that the extent to which these savings can be expected depends on the accuracy of the estimated distribution between patients using cinnarizine with dimenhydrinate for vertigo caused by Ménière's disease and patients using it for vertigo caused by other disorders.

Twenty-four publications on ELSO issues were included. In the ethical domain, the challenges with diagnosis and treatment were discussed. Several ethical constraints arise from these challenges, including delayed and ineffective treatment of symptoms, reduced quality of life of patients, financial burden and strain on the patient-physician relationship. Driving restrictions for patients with Ménière's disease and vertigo were considered potential legal issues. In Switzerland, drugs can only be placed on the Spezialitätenliste if drugs are licensed by Swissmedic and are effective, appropriate, and economically efficient. Social issues found in the literature considered the impact on a patient's social network and society as a whole. More specifically, patients with Ménière's disease suffered from reduced quality of life, depressive symptoms, social isolation and participation restrictions. Finally, in the organisational domain, the need for a holistic approach was advocated in the literature, which requires input from various healthcare professionals and thereby potentially complicating the organisation of treatment pathways.

CONCLUSION

The evidence base was limited. The clinical evidence in adult patients with Ménière's disease suggests little or no difference in the treatment effect of betahistine compared with placebo on vertigo attack frequency (1 RCT; moderate certainty evidence), tinnitus intensity (1 RCT; low certainty evidence), hearing loss (1 RCT; low certainty evidence), and disease-specific HRQoL (1 RCT; moderate certainty evidence). Betahistine may improve disease-specific HRQoL compared with no treatment in patients with Ménière's disease, but the evidence is very uncertain (1 RCT; very

low certainty evidence). Betahistine may be well tolerated in patients with Ménière's disease, with little or no difference in the occurrence of serious adverse events compared to placebo (2 RCTs; low certainty evidence). In adult patients with diverse vertigo aetiologies the evidence on the effect of betahistine on vertigo compared with placebo is lacking, seems not consistent and is very uncertain (3 RCTs; very low certainty evidence). Betahistine may be well tolerated in patients with vertigo, with no serious adverse events encountered with betahistine or placebo treatment, but the evidence is very uncertain (3 RCTs; very low certainty evidence). In adult patients with idiopathic subjective tinnitus cinnarizine may show little or no difference in tinnitus symptoms compared with placebo, but the evidence is very uncertain (1 RCT; very low certainty evidence). No data was reported on serious adverse events. In adult patients with diverse vertigo aetiologies cinnarizine with dimenhydrinate treatment probably results in an improvement of vertigo symptoms compared to placebo (2 RCTs; moderate certainty evidence). Cinnarizine with dimenhydrinate may be well tolerated in patients with vertigo, with no serious adverse events encountered with cinnarizine with dimenhydrinate or placebo treatment (2 RCTs; low certainty evidence).

From a health economic perspective, cinnarizine with dimenhydrinate was estimated to dominate no treatment (lower costs, more effects) in the treatment of vertigo caused by other disorders than Ménière's disease. Over a 5-year period, the budget impact showed that cinnarizine with dimenhydrinate for the treatment of Ménière's disease and vertigo caused by other disorders than Ménière's disease was associated with projected budget savings of CHF 1.2 million. Cost-effectiveness was not assessed for betahistine or cinnarizine without dimenhydrinate for the treatment of Ménière's disease, vertigo or tinnitus, due to a lack of evidence for a positive treatment effect in the clinical review. Despite the lack of evidence for a positive treatment effect of betahistine and cinnarizine, these treatments are currently reimbursed in Switzerland, and hence associated with a budgetary impact. Over a 5-year period, the budget impact of betahistine was projected to be CHF 17.2 million, for cinnarizine without dimenhydrinate projected to be CHF 0.8 million. Finally, the treatment of Ménière's disease, vertigo and tinnitus was associated with several ethical, legal, social and organisational issues, including issues with diagnosis of disease, effects on patient's quality of life and social interactions and the organisation of care.

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Abbreviations and acronyms

AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery
AUVP	Acute Unilateral Vestibulopathy
AICA	Anterior inferior cerebellar artery
aMD	Adjusted mean difference
BI	Budget impact
BPPV	Benign paroxysmal positional vertigo
CDA	Canada's Drug Agency
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CE plane	Cost-effectiveness plane
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence interval
dB	Decibel
DHI	Dizziness handicap inventory
EUnetHTA	European Network for Health Technology Assessment
FLS	Functional level score
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
Hz	Hertz
ICER	Incremental cost-effectiveness ratio
ICER-US	Institute for Clinical and Economic Review
ITD	Intratympanic dexamethasone
MCID	Minimal clinically important difference
MD	Mean difference
mg	Milligram
MiniTF12	Mini-tinnitus impairment questionnaire score based on 12 items
ml	Millilitre
MVS	Mean Vertigo Score
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
OWSA	One-way sensitivity analysis
PICO	Population, intervention, comparator and outcome
PRISMA	Preferred Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PTA	Pure tone audiometry
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RoB 2	Revised Cochrane Risk of Bias tool for randomised trials

RR	Risk ratio
SAE	Serious adverse event
TIA	Transient ischemic attack
UK	United Kingdom
USA	United States of America
VBI	Vertebrobasilar insufficiency
VDADL	Vestibular disorders activities of daily living
ZIN	National Health Care Institute

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy question and context

Ménière's disease is a disorder of the inner ear that can cause various symptoms, including vertigo, tinnitus, hearing loss and aural fullness.[1] In Switzerland, betahistine (an analogue of histamine) and cinnarizine (a selective calcium channel blocker and an antihistamine) are reimbursed for patients experiencing symptoms of vertigo, tinnitus and hearing loss caused by Ménière's disease or other disorders. Furthermore, cinnarizine with dimenhydrinate (an antihistamine with anticholinergic [antimuscarinic] properties, exerting parasympatholytic and central depressant effect) is reimbursed for the symptomatic treatment of transient vertigo.[2]

Within the context of the Federal Office of Public Health (FOPH) HTA Program, the evidence for these coverage decisions is to be re-evaluated. This HTA report presents the best available evidence regarding the application of betahistine and cinnarizine with or without dimenhydrinate for the treatment of vertigo, tinnitus and/or hearing loss caused by Ménière's disease or for the treatment of vertigo or tinnitus caused by other peripheral or central vestibular disorders. 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.

2. Medical background

Ménière's disease was named after the French physician Prosper Ménière who described the symptoms in a patient following intralabyrinthine haemorrhage in 1861.[3] In the past, the term Ménière's syndrome has been used in case symptoms occurred secondary to a known underlying cause, while Ménière's disease has been used for those cases where the cause is (yet) unknown.[4,5] The use of this terminology has not been consistent though and the terms are often used interchangeably.[5] An increase in the volume of fluid in the inner ear (i.e. endolymphatic hydrops) is associated with the disease, but this does not explain all symptoms of the disease.[1]

Ménière's disease is characterised by episodes of vertigo, tinnitus, hearing loss and aural fullness. Vertigo is the sensation of self-motion when no motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement; the term includes spinning vertigo and non-spinning vertigo.[6] Tinnitus consists of a constant or intermittent ringing or other noise in the ear or in the head. Aural fullness is a feeling of pressure deep inside the ear.

The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) created a strict clinical classification to diagnose Ménière's disease.[7–9] These criteria were revised by the Classification Committee of the Bárány Society together with different national and international organisations in 2015, and approved by the AAO-HNS Equilibrium Committee.[1,10] The revisions distinguish definite from probable Ménière's disease and are defined as follows: "The diagnosis of definite Ménière's disease is based on clinical criteria and requires the observation of an episodic vertigo syndrome associated with low- to medium-frequency sensorineural hearing loss and fluctuating aural symptoms (hearing, tinnitus and/or fullness) in the affected ear".[1] The disease is associated with 2 or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours. "Probable Ménière's disease is a broader concept defined by episodic vestibular symptoms (vertigo or dizziness) associated with fluctuating aural symptoms occurring in a period from 20 minutes to 24 hours."[1] The disease is most common between the ages of 30 and 60 years. In Europe, the incidence is estimated to be 50 to 200 per 100,000 adults per year.[11]

Symptoms of Ménière's disease frequently overlap with those of other disorders or syndromes.[12,13] For example, only 4% to 10% of cases of vertigo are caused by Ménière's disease.[14] Benign paroxysmal positional vertigo (BPPV) and Acute Unilateral Vestibulopathy (AUVP), also known as vestibular neuronitis, are considered to be the most common (peripheral) causes of vestibular vertigo. BPPV is characterized by brief episodes of vertigo triggered by changes in head position, whereas AUVP involves a sudden, severe onset of vertigo often associated with a preceding viral infection. Both BPPV and AUVP can present with vertigo similar to that of Ménière's disease, but they typically lack the fluctuating hearing loss and tinnitus seen in Ménière's patients.[15] The main diagnostic difference for BPPV is the duration of symptoms (usually shorter than 1 minute) and positive triggers. Other causes of vertigo and tinnitus include vestibular migraine, vertebrobasilar insufficiency (VBI), transient ischemic attack (TIA), anterior inferior cerebellar artery (AICA) infarct,

and labyrinthine artery infarct. Vestibular migraine is a neurological disease in which patients suffer from a combination of migraine headache and vestibular symptoms, such as vertigo, imbalance and nausea. VBI is a condition characterized by reduced blood flow to the back part of the brain, potentially causing various symptoms including vertigo. A TIA is a brief period of neurological dysfunction resultant from a short interruption in blood flow to part of the brain, potentially leading to various symptoms including vertigo. An AICA infarct is a type of stroke affecting the AICA and can lead to inner ear problems like vertigo and hearing loss. In a labyrinthine artery infarct, the blood flow to the inner ear structures is disrupted, potentially leading to symptoms that include vertigo, nausea and vomiting. Since patients with different causes of vertigo respond differently to treatment, differentiating between different causes is important.

At the onset of the disease Ménière's disease usually affects only one ear, but some patients experience symptoms in both ears.[16,17] The fraction of patients with bilateral symptoms increases with the duration of the disease (up to 47% after 20 years).[18] The natural course of Ménière's disease is typically progressive, with symptoms fluctuating over time. Usually, there is a gradual deterioration in hearing, and a progressive loss of balance function, leading to chronic dizziness.[19] Because of the unpredictable nature of symptoms and the occurrence of severe, disabling vertigo attacks, patients with Ménière's disease often have a reduced quality of life (QoL). [19,20]

Various treatment options are available for patients with the disease, including medical and surgical treatments. Although none of the treatments can cure Ménière's disease, they may reduce the frequency and severity of the vertigo attacks and improve QoL.[16] Typically, diuretics (also known as water pills) and betahistine are recommended by the AAO-HNS, as first-line treatments.[16] The AAO-HNS recommendations did not describe any factors that affected effects of these treatments. Intratympanic corticosteroids or gentamicin, and surgical treatments (ranging from conservative to destructive) can be considered in subsequent treatment lines.[12,13,21]

3. Technology

Table 1 lists the indications for betahistine and cinnarizine with or without dimenhydrinate, for which these medications are reimbursed in Switzerland.[2] In this HTA report, the scope of vertigo is restricted to vertigo caused by peripheral or central vestibular disorders (hereafter: vestibular vertigo) to ensure its direct association with the vestibular system. Since vertigo and tinnitus are general symptoms with various possible underlying causes, specific conditions were further defined based on the output of the systematic literature searches and discussion with Swiss clinical experts. Additionally, ***Table 1*** shows the mode of application and dosing of betahistine and cinnarizine with or without dimenhydrinate.

Table 1. Indications for betahistine and cinnarizine with or without dimenhydrinate

Medication	Licensed indications for which the medication is reimbursed in Switzerland[2]	Specific conditions (based on the output of the systematic literature searches and Swiss expert opinion)	Mode of application	Licensed dosing
Betahistine	– Vertigo caused by problems with blood flow to the inner ear – Ménière's syndrome and Ménière-like syndromes (vertigo, tinnitus, hearing loss)	– Vestibular migraine with the presence of symptoms of the inner ear – VBI – TIA – AICA infarct – Labyrinthine artery infarct	– Tablets – Oral drops	– Tablets: 24 mg (8 mg tid) or 48 mg (16 mg tid or 24 mg bid) – Oral drops: 3x 1-2 ml (24-48 mg) qd or 2x 3 ml (48 mg) qd
Cinnarizine	– Irritation and circulatory disorders of the labyrinth – Cochlear and vestibular disorders: tinnitus, vertigo, nystagmus, along with associated nausea, sweating and vomiting – Ménière's disease	– Vestibular migraine – BPPV – VBI – TIA – AICA infarct – Labyrinthine artery infarct	– Capsules – Oral drops	– Capsules: 1 capsule (75 mg) qd – Oral drops: 8 drops (24 mg) tid
Cinnarizine with dimenhydrinate	Symptomatic treatment of transient vertigo (up to a maximum of 4 weeks)	– Vestibular migraine – BPPV – VBI – TIA – AICA infarct – Labyrinthine artery infarct	Tablets	1 tablet (20 mg cinnarizine and 40 mg dimenhydrinate) tid

Abbreviations
AICA = anterior inferior cerebellar artery, bid = bis in die (twice a day), BPPV = benign paroxysmal positional vertigo, mg = milligram, ml = millilitre, qd = quaque die (once a day), TIA = transient ischemic attack, tid = ter in die (3 times a day), VBI = vertebrobasilar insufficiency.

3.1 Technology description

3.1.1 Betahistine

The recommended dose of betahistine for adults is 24 milligrams (mg) to 48 mg per day. It usually takes days to weeks before any response to betahistine is noticeable. Contraindications are hypersensitivity to the active substance or any of the components present in the medication. Furthermore, patients with pheochromocytoma should not be treated with betahistine.[2]

3.1.2 Cinnarizine

For cinnarizine, the recommended dose for adults is 75 mg per day. In order to achieve an optimal and lasting therapeutic effect, it may be necessary to prolong the use of cinnarizine for a longer duration, for example, at least 4 weeks.[2] Cinnarizine should not be prescribed to patients with extrapyramidal symptoms, parkinsonism or a history of depression. Additionally, it should not be used after a recent heart attack or if patients are hypersensitive to the active ingredient or any other component of the medication.[2]

3.1.3 Cinnarizine with dimenhydrinate

The recommended dose for adults is 20 mg of cinnarizine and 40 mg of dimenhydrinate, taken 3 times a day. The contraindications listed for cinnarizine without dimenhydrinate also apply to cinnarizine with dimenhydrinate. Additional contraindications exist for the combination, such as angle-closure glaucoma, urinary retention, raised intracranial pressure, convulsions and alcohol abuse.[2]

3.2 Alternative technologies

Various treatment options are available for patients with Ménière's disease, including medical and surgical treatments. Typically, diuretics (also known as water pills) and betahistine are recommended by the AAO-HNS, as first-line treatments.[16] Relevant alternatives for betahistine, cinnarizine and/or cinnarizine with dimenhydrinate are further described in ***Section 9.1***.

3.3 Regulatory status / provider

The specific indications for which betahistine, cinnarizine and cinnarizine with dimenhydrinate are reimbursed in Switzerland are presented in ***Table 1***. Briefly, both betahistine and cinnarizine are reimbursed for patients experiencing symptoms of vertigo, tinnitus and hearing loss caused by Ménière's disease or other disorders. Cinnarizine with dimenhydrinate is reimbursed for the symptomatic treatment of transient vertigo.[22,23]

4. Population, Intervention, Comparator, Outcome (PICO)

The PICO for this HTA, which was specified in collaboration with Swiss clinical experts, is outlined in ***Table 2***. Patients under 18 years of age are considered out of scope, because betahistine and cinnarizine with dimenhydrinate are not recommended in Switzerland for use in children and adolescents due to insufficient evidence regarding the safety and efficacy of these drugs.[2] For cinnarizine information on dosages is provided for adults only.[2]

Table 2. PICO

Population	Adult patients with Ménière's disease and adult patients with other peripheral or central vestibular disorders experiencing symptoms of vestibular vertigo and/or tinnitus
Intervention	– Betahistine[a,b] – Cinnarizine[a] – Cinnarizine with dimenhydrinate[a,c]
Comparator	– Placebo[a] – No treatment[a]
Outcome	Efficacy and effectiveness[d] – Primary outcomes - Vertigo[e] - Tinnitus - Hearing – Secondary outcomes - Disease-specific HRQoL - HRQoL Safety – Primary outcome - Serious adverse events[f] – Secondary outcome - Other adverse events[g] Economics – Incremental/total costs, life years and QALYs – ICER – Budget impact

Abbreviations
HRQoL = health-related quality of life, ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years.
Notes
a = The interventions could also be evaluated together with co-interventions as long as these co-interventions are identical with those in the comparator arm.
b = Tinnitus in patients not suffering from Ménière's disease is not a licensed indication for betahistine and therefore not included in the PICO-question of this report
c = Cinnarizine with dimenhydrinate is licensed only for the symptomatic treatment of transient vertigo; this intervention is therefore not relevant for all subpopulations.
d = For subpopulations the outcomes of interest might differ, e.g. tinnitus is the only relevant outcome when evaluating cinnarizine in adult patients experiencing symptoms of tinnitus without experiencing any other Ménière-like symptoms such as vestibular vertigo.
e = The frequency (e.g. number of attacks per month), severity and duration of attacks were assessed.
f = Including any event that causes death, is life-threatening, requires hospitalisation, results in disability or permanent damage or in congenital abnormality; measured as the number of participants who experienced at least one serious adverse event during the follow-up period.
g = Including headache, gastrointestinal disturbance (including nausea, indigestion, abdominal pain or diarrhoea), sleep disturbance (including drowsiness or insomnia) or dry mouth; measured as the number of participants who experienced at least one episode of the specified adverse events during the follow-up period.

5. HTA research questions

For the evaluation of the technology, the following research questions covering central HTA domains (i.e. clinical effectiveness, safety, cost-effectiveness, budget impact, ethical, legal, social and organisational aspects), as designated by the European Network for Health Technology Assessment (EUnetHTA) Core Model, were 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. Is the technology cost-effective compared to the comparator technology?
5. Are there ethical, legal, social or organisational issues related to the technology?

6. Efficacy, effectiveness and safety

Summary statement efficacy, effectiveness and safety

In the clinical systematic review 10 RCTs were included on licensed use of betahistine or cinnarizine with or without dimenhydrinate for vertigo, tinnitus and hearing loss caused by Ménière's disease or for vertigo and tinnitus caused by other peripheral or central vestibular disorders. Some of these RCTs missed relevant outcome data for valid data interpretation; these results are presented in an appendix to provide full insight in published RCT evidence. The evidence base was limited.

Betahistine for Ménière's disease

In adult patients with Ménière's disease treated with betahistine versus placebo no statistically significant differences were found in vertigo attack frequency (1 RCT; moderate certainty evidence), tinnitus intensity (1 RCT; low certainty evidence), hearing loss (1 RCT; low certainty evidence), and disease-specific health-related quality of life (HRQoL) assessed with 3 different questionnaires (1 RCT; moderate certainty evidence). A statistically significant improvement in disease-specific HRQoL assessed with the dizziness handicap inventory was reported for betahistine compared to no treatment (1 RCT; very low certainty evidence). No statistically significant difference was found in the occurrence of serious adverse events for betahistine versus placebo in patients with Ménière's disease (2 RCTs; low certainty evidence).

Betahistine for vertigo

In adult patients with diverse vertigo aetiologies treated with betahistine versus placebo the results for 3 different vertigo outcomes were lacking and seem not consistent. Compared to baseline, betahistine treatment resulted in a statistically significant decrease in vertigo attack frequency (1 RCT; very low certainty evidence) and vertigo attack severity (2 RCTs; very low certainty evidence) versus a statistically significant decrease for placebo treatment in vertigo attack duration (1 RCT; very low certainty evidence). No statistically significant difference was found in investigator-reported vertigo symptoms for betahistine versus placebo (1 RCT; very low certainty evidence). No data was reported on HRQoL. No serious adverse events were encountered in the treatment with betahistine or placebo (3 RCTs; very low certainty evidence).

Cinnarizine for tinnitus

In adult patients with idiopathic subjective tinnitus treated with cinnarizine versus placebo no statistically significant differences were found in tinnitus disturbance during activity or rest nor in

patient-reported tinnitus symptoms (1 RCT; very low certainty evidence). No data was reported on HRQoL or serious adverse events.

Cinnarizine with dimenhydrinate for vertigo

In adult patients with diverse vertigo aetiologies treated with cinnarizine with dimenhydrinate the vertigo symptoms statistically significantly improved compared to placebo, assessed with the mean vertigo score (2 RCTs; moderate certainty evidence). A statistically non-significant improvement of patient and investigator-reported vertigo symptoms was found (2 RCTs; very low certainty evidence). No data was reported on HRQoL. No serious adverse events were encountered in the treatment with cinnarizine with dimenhydrinate or placebo (2 RCTs; low certainty evidence).

6.1 Methodology efficacy, effectiveness and safety

The systematic review methodology described in this HTA report is developed in line with the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.4) and the report is drafted in adherence to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[22,23] The systematic review was conducted following a review protocol, which is published on the FOPH website.[24]

6.1.1 Databases and search strategy

The focus of this HTA was to search for the highest level of available scientific evidence provided by randomised controlled trials (RCTs). The primary systematic literature search for RCTs was conducted on 9 November 2023. The evidence base on this topic is largely build on older studies. A common limitation of older studies compared to more recent studies is poor reporting of the methodology and results, also resulting in lower study quality. Since data reporting in the included RCTs (i.e. the study design with the highest level of evidence) was limited, it was not expected that a search for comparative non-randomised studies would result in additional relevant evidence. Instead, it was decided during the project to include RCTs with relevant data missing for valid data interpretation in the clinical systematic review and report these results in an appendix, to provide full insight in published RCT evidence. Systematic literature searches were conducted in 3 databases: PubMed (MEDLINE), Embase.com and the Cochrane Library. To gain insight in ongoing RCTs with study characteristics in line with the PICO of this HTA, searches were conducted on the websites of ClinicalTrials.gov (https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu) on 11 December 2023.

The search strategy was developed with an information specialist based on the PICO reported in ***Chapter 4***. As quality control the search strategies were checked by a second researcher and

validated with a set of key articles. Search strings were compiled for the population with Ménière's disease, for the symptoms of vestibular vertigo and/or tinnitus (to search for populations with other peripheral or central vestibular disorders experiencing symptoms of vestibular vertigo and/or tinnitus), and for the interventions betahistine or cinnarizine with or without dimenhydrinate. A search limit was added to exclude conference abstracts and preprints. No other search limits were applied; studies were selected by applying pre-specified eligibility criteria during the selection process.

Since vertigo and tinnitus are general symptoms with various possible underlying causes, Swiss clinical experts were consulted to check whether studies identified during the primary systematic literature search on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fell within the scope of the licensed indications of the interventions. Based on the output of the primary systematic literature search and expert opinion an additional systematic literature search was performed on 29 January 2024 for betahistine and cinnarizine with or without dimenhydrinate for the most common indications that fall within the scope of the licensed indications, i.e. vestibular migraine, VBI, TIA, AICA infarct, and labyrinthine artery infarct; and the indication BPPV for cinnarizine with or without dimenhydrinate. See ***Table 1*** for an overview of the indications.

The syntax of the search strategies was composed for one medical database, PubMed (MEDLINE), and customised to the other databases. The details of the search strategies are outlined in ***Appendix A.***

Electronic records of the articles retrieved by the searches were stored by using Endnote reference manager software (Clarivate Analytics, United States of America [USA]). This Endnote file was uploaded in Rayyan software (Rayyan Systems Inc., USA) for the selection of the articles.[25] Duplicate records were deleted, and this number was registered in the PRISMA flow diagrams.

6.1.2 Other sources

Reference lists of systematic reviews relevant to the research question identified during the title and abstract screening were checked for potentially relevant additional references of primary studies. The systematic review itself was excluded after the reference check. Narrative reviews were excluded directly and not checked for references.

In addition, the supplementary search technique backward citation chasing was applied, i.e. by finding other studies cited within the included articles. All the additionally found primary studies were assessed based on the pre-specified eligibility criteria.

6.1.3 Study selection

Relevant articles were selected in duplicate by a systematic approach by 2 independent researchers. Firstly, the potential relevancy of the articles was assessed during the title/abstract screening.

Potentially relevant articles were selected for full-text screening, all other articles were excluded, without documenting the reason for exclusion. If the 2 researchers disagreed on the relevance of an article, this was discussed. If disagreements between the 2 researchers during title/abstract screening were not resolved, the article was assessed in full text. Secondly, the articles were assessed in full text based on the pre-specified eligibility criteria (see Table 3). Articles were included in the systematic review if they fulfilled the inclusion criteria; the remaining articles were excluded and the primary reason for exclusion was listed. Any disagreements between the 2 researchers were resolved by discussion, if needed a third researcher was consulted.

The search results were screened against the pre-specified eligibility criteria, covering elements of the article, study design and PICO. The eligibility criteria table in the HTA protocol was updated during the project with more detailed criteria for the population other peripheral or central vestibular disorders, based on the output of the primary systematic literature search and Swiss expert opinion (see ***Table 1***). Indications which were out of scope under the Swiss licensing were excluded during the full-text selection with a documented reason for exclusion. Furthermore, it was decided to select studies on off-label use on the medications of interest and report these studies in ***Chapter 9. Additional issues***.

To provide insight in the details of the selection process, PRISMA flow diagrams with the results of the study selection and a table with the primary reasons for exclusion for each excluded article at full-text review were composed.

Table 3. Eligibility criteria for the clinical systematic literature search

	Inclusion criteria	Exclusion criteria
Publication year	All	None
Language of publication	English, French, German, Italian	All other languages
Country of study	Worldwide	None
Study design/ publication type	- RCTs - Comparative non-randomised studies (i.e. prospective or retrospective cohort studies)[a]	– Systematic reviews (only used for a reference check) – Narrative reviews Non-comparative studies (e.g.single-arm trials) – Cross-over trials, without data before cross-over – Simulation studies – Case series or case reports – Irrelevant publication types (e.g. letter, comment, expert opinion, – editorial, abstract only, conference presentation, book chapter and preprints)
Population	– Adult patients with Ménière's disease or Ménière's syndrome[b] – Adult patients with other peripheral or central vestibular disorders experiencing symptoms of vestibular vertigo[c] – Adult patients with other peripheral or central vestibular disorders experiencing symptoms of tinnitus[d]	– Animal studies – Patients aged <18 years – Patients who had already undergone destructive medical (e.g. intratympanic gentamicin) or surgical treatment (e.g. endolymphatic sac surgery, labyrinthectomy and vestibular neurectomy) – Other causes of vertigo (e.g. non-neurological causes of vertigo, such as anxiety disorders or cardiac disease) – Other peripheral or central vestibular disorders which are out of scope for coverage for betahistine and cinnarizine with or without dimenhydrinate under the Swiss licensing[e]
Intervention	- Betahistine[f] - Cinnarizine[f] - Cinnarizine with dimenhydrinate[f]	Other interventions
Comparator	- Placebo[f] - No treatment[f]	– Other comparators – No comparator
Outcome	- Vertigo - Tinnitus - Hearing - Disease-specific HRQoL - HRQoL - Serious adverse events[g] - Other adverse events[h]	- Studies with duplicate data (study with the largest sample size or most extended follow-up would be included for data extraction of the results)[i] - Other outcomes
Other		Inadequate data (e.g. missing relevant data or unexplained important errors in patient flow)[j]

Abbreviations
HRQoL = health-related quality of life, RCTs = randomised controlled trials.
Notes
a = These studies were included in case less than 2 RCTs were found.
b = Although the term Ménière's syndrome is nowadays not often used, this term has been used formerly and therefore studies in patients with Ménière's syndrome were included.
c = Other indications betahistine: vestibular migraine with the presence of symptoms of the inner ear, vertebrobasilar insufficiency (VBI), transient ischemic attack (TIA), anterior inferior cerebellar artery (AICA) infarct, labyrinthine artery infarct; Other indications cinnarizine: vestibular migraine, benign paroxysmal positional vertigo (BPPV), VBI, TIA, AICA infarct, labyrinthine artery infarct; Other indications cinnarizine with dimenhydrinate: vestibular migraine, BPPV, VBI, TIA, AICA infarct, labyrinthine artery infarct.
d = Other indications cinnarizine: vestibular migraine, BPPV, VBI, TIA, AICA infarct, labyrinthine artery infarct.
e = Swiss clinical experts were consulted in order to check whether studies identified on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fell with-in the scope of the licensed indications of the interventions. For betahistine studies in populations with the following conditions or symptoms were excluded because they did not fall within the scope of its licensed indications: BPPV, tinnitus not due to Ménière's disease or vestibular symptoms, surgery-induced acute vestibular syndrome, tinnitus due to either blast injury or noise-induced hearing loss.
f = The interventions could also be evaluated together with co-interventions as long as these co-interventions were identical with those in the comparator arm.
g = Including any event that causes death, is life-threatening, requires hospitalisation, results in disability or permanent damage

or in congenital abnormality; measured as the number of participants who experienced at least one serious adverse event during the follow-up period.
h = Including headache, gastrointestinal disturbance (including nausea, indigestion, abdominal pain or diarrhoea), sleep disturbance (including drowsiness or insomnia), dry mouth; measured as the number of participants who experienced at least one episode of the specified adverse events during the follow-up period.
i = If applicable, unique results from interim studies would be included (e.g. when HRQoL results are reported only in an interim study), and interim studies might be used as additional input on the study methodology.
j = A specific exclusion criterion was formulated to be transparent on the details of the inadequate data and reported in the table with excluded studies found with the clinical systematic literature search for RCTs: Inadequate data (incomplete data).

6.1.4 Assessment of quality of evidence

6.1.4.1 Risk of bias of the reported outcomes in the included studies

The included studies were critically appraised by one researcher and fully reviewed by and discussed with a second researcher. The risk of bias of the reported outcomes in the RCTs was assessed with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2) for the primary efficacy outcomes vertigo, tinnitus and hearing, secondary efficacy outcome HRQoL, and for the primary safety outcome serious adverse events.[22,25] The primary efficacy outcomes of interest differed for the 4 groups stratified based on medication and population: betahistine for Ménière's disease (vertigo, tinnitus, hearing), betahistine for vertigo (vertigo), cinnarizine for tinnitus (tinnitus), and cinnarizine with dimenhydrinate for vertigo (vertigo). The risk of bias was visualised in plots with the web application Robvis.[27]

For results reported on outcomes with relevant data missing for valid data interpretation (i.e. missing results for a study arm or missing pre-treatment data) the risk of bias was not assessed.

6.1.4.2 Overall certainty of the evidence

The overall certainty of the evidence on outcome level was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[22,27] The certainty of a body of evidence is defined as the extent to which one can be confident that the estimated effect of an intervention is close to the true effect. A GRADE assessment of this certainty involved appraisal of 5 domains: (1) risk of bias (i.e. study limitations; as assessed with the RoB 2 tool), (2) inconsistency (i.e. heterogeneity or variability in the estimates of treatment effect across studies), (3) indirectness of evidence (i.e. the degree of differences between the PICOs of this HTA and the PICOs of the primary studies), (4) imprecision of the effect estimates, and (5) the risk of publication bias. Based on the assessments for each domain, the overall evaluation of the certainty of the evidence per outcome was classified as high, moderate, low or very low. The overall certainty of the evidence was summarised in GRADE summary of findings tables for each group, together with key information concerning the illustrative comparative risks, relative effects of the intervention, and the amount of available evidence.[22,27] GRADEpro GDT software (Evidence Prime Inc., Canada) was used to construct the summary of findings tables for the primary and secondary efficacy outcomes (i.e. vertigo, tinnitus, hearing, disease-specific HRQoL, HRQoL) and the primary safety outcome (i.e. serious adverse events).[28]

6.1.5 Methodology data extraction, analysis and synthesis of the domains efficacy, effectiveness and safety

6.1.5.1 Data extraction

Relevant data from the included studies found in the medical journal databases was extracted by one researcher into a standardised data-extraction spreadsheet in Microsoft Excel and fully reviewed by a second researcher. This spreadsheet included:

– bibliographic reference;

– study characteristics: study design, study objective, country, setting, study period, length of follow-up, inclusion/exclusion criteria and source of funding;

– study population: diagnosis, unilateral or bilateral, sample size, age, sex, comorbidities and comedication;

– intervention: dose and duration;

– comparator: placebo or no treatment;

– outcomes: vertigo, tinnitus, hearing, disease-specific health-related QoL (HRQoL), HRQoL, serious adverse events and other adverse events;

– additional comments: study limitations or issues that need to be considered for data interpretation.

Details of ongoing RCTs found in ClinicalTrials.gov and the European Union Clinical Trials Register were extracted and summarised in a Microsoft Word table:

– study identifier;

– status, e.g. recruiting and not yet recruiting;

– country;

– study period;

– enrolment: estimated and actual;

– population;

– intervention;

– comparator;

– outcomes;

– estimated time of completion of the trial.

6.1.5.2 Data analysis and synthesis

The extracted data of the included RCTs was summarised in study characteristics tables, risk of bias tables/figures, summary tables, and GRADE summary of findings tables. These tables were reviewed by a second researcher. The options for clinically relevant data stratification were discussed with the HTA team, the FOPH and clinical experts. Based on the heterogeneity of the medication and study populations in the included RCTs, the results were stratified in 4 groups: 1) betahistine for Ménière's disease, 2) betahistine for vertigo, 3) cinnarizine for tinnitus, and 4) cinnarizine with dimenhydrinate for vertigo. When RCTs studied solely a population with Ménière's disease or reported stratified data for the subpopulation with Ménière's disease, these studies were analysed in the group Ménière's disease. RCTs in populations with undefined vertigo or vertigo with diverse causes (i.e. this includes RCTs with unstratified data for Ménière's disease) were analysed in the group vertigo.

It was not possible to calculate pooled estimates for most outcomes, due to lacking reporting of results in the studies, the low number of studies per outcome, and the occurrence of zero events in the intervention as well as the comparator arms within studies. These outcomes were analysed narratively and presented in summary tables. When event rates and sample sizes were reported per study arm (i.e. for the outcome serious adverse events and number of participants with improvement in vertigo or tinnitus) the risk ratio and 95% confidence interval was calculated with the Comprehensive Meta-Analysis software (Biostat, USA).[29] A pooled risk ratio, 95% confidence interval, and heterogeneity statistics were calculated by meta-analysis using a random-effects model (i.e. DerSimonian and Laird). When the mean treatment difference between the study arms was not reported, an absolute mean difference was calculated based on the mean absolute change in the intervention and comparator arm.

Results reported on outcomes with relevant data missing for valid data interpretation (i.e. missing results for a study arm or missing pre-treatment data) were not included in the data synthesis. The extracted data of these results with missing data is enclosed in ***Appendix A.***

6.2 Results efficacy, effectiveness and safety

6.2.1 PRISMA flow diagram

6.2.1.1 Primary systematic literature search

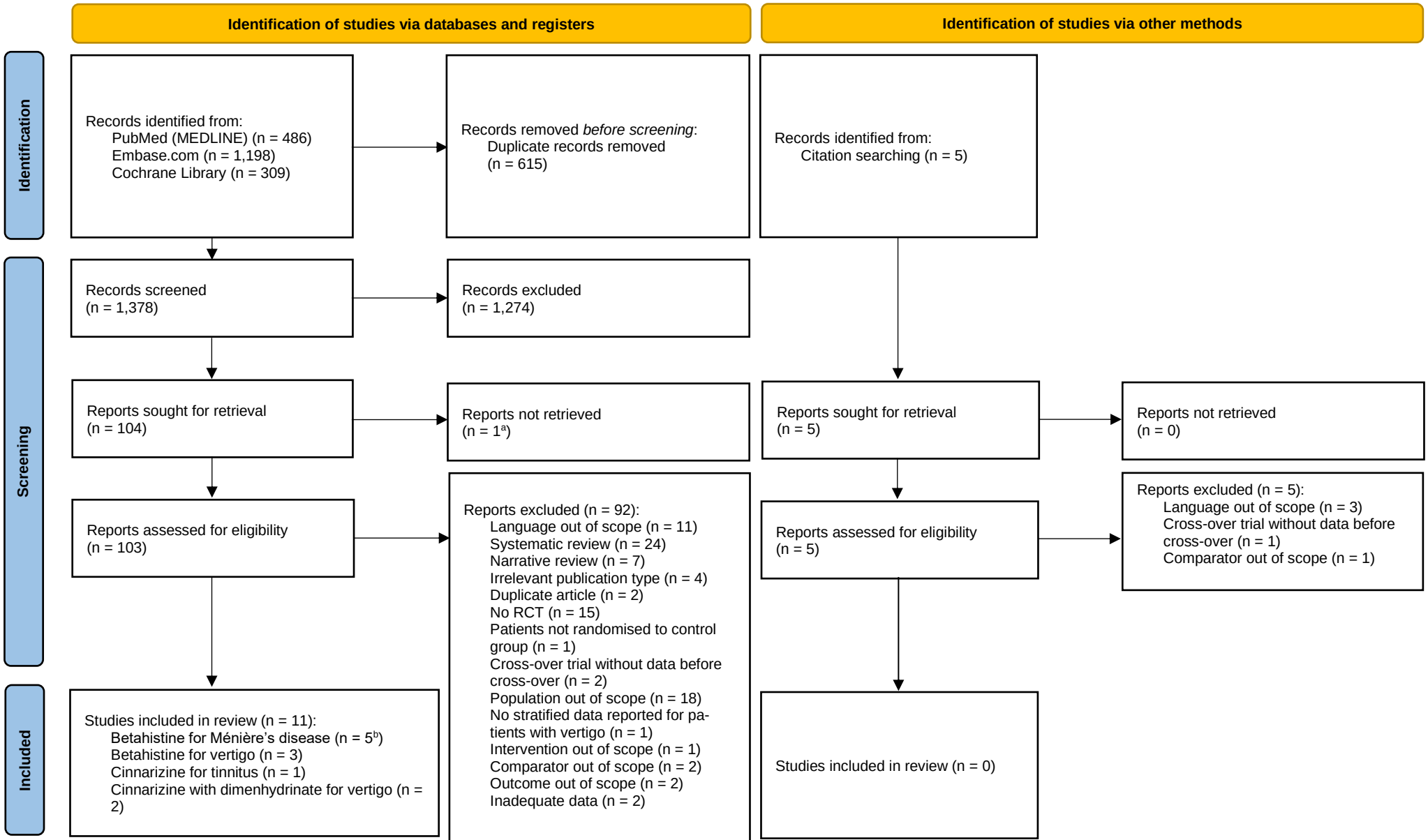
The results of the primary systematic literature search for RCTs are summarised in ***Figure 1.*** In total, 1,378 unique records were identified in PubMed (MEDLINE), Embase.com and the Cochrane Library with the search conducted on 9 November 2023. Of those, 1,274 records were excluded based on title and abstract, leaving 104 articles for full-text assessment. One systematic review could not be retrieved, however 2 more recent systematic reviews of these authors were included and used for a reference check.[30–32] Of the 103 articles assessed for eligibility, 92 articles were

excluded. Most important reasons for exclusion were systematic reviews excluded after the reference check (24 articles), population out of scope (18 articles), no RCT (15 articles), language out of scope (11 articles), and narrative review (7 articles). An overview of the more detailed reasons for exclusion by each excluded article is enclosed in ***Appendix B.***

A total of 11 RCTs were included in the systematic review with clinical evidence on betahistine or cinnarizine with or without dimenhydrinate for vertigo, tinnitus and hearing loss caused by Ménière's disease or for vertigo and tinnitus caused by other peripheral or central vestibular disorders. Based on the medication and population the data in this HTA is stratified in 4 groups: betahistine for Ménière's disease (5 RCTs[22,23,25–27]), betahistine for vertigo (3 RCTs[33–35]), cinnarizine for tinnitus (1 RCT[36]), and cinnarizine with dimenhydrinate for vertigo (2 RCTs[37,38]). Of the 5 RCTs on betahistine for Ménière's disease, 3 RCTs reported data on licensed use of betahistine, one RCT on licensed and off-label use of betahistine, and one RCT on off-label use. The other RCTs on betahistine for vertigo and cinnarizine with or without dimenhydrinate concerned licensed use.

In addition, 5 records were identified by citation searching of relevant systematic reviews and the included RCTs. These articles were assessed for eligibility and all were excluded, for the reasons language out of scope (3 articles), cross-over trial without data before cross-over (1 article), and comparator out of scope (1 article).

Figure 1. PRISMA flow diagram of the primary clinical systematic literature search for RCTs

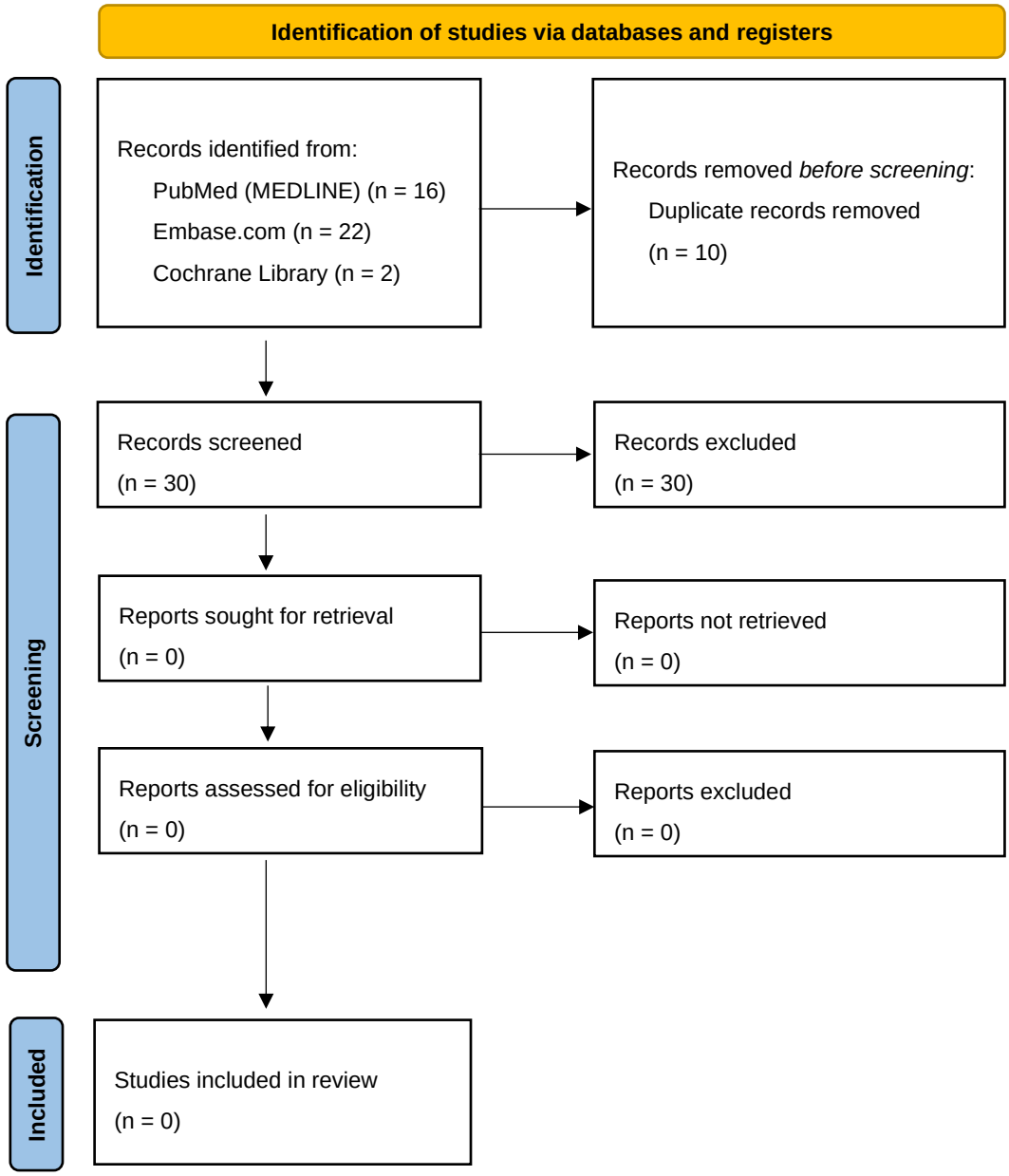


Abbreviations
PRISMA = Preferred Items for Systematic Reviews and Meta-Analyses, RCT= Randomised controlled trial
Notes
Search date 9 November 2023.
a = Reference: Savage et al Tinnitus. BMJ clinical evidence. 2007; 2 more recent systematic reviews of Savage et al were included in the title/abstract selection and retrieved.
b = 3 studies reported data on licensed use of betahistine for Ménière's disease, 1 study on licensed and off-label use of betahistine, and 1 study on off-label use of betahistine. All other studies are licensed use

6.2.1.2 Additional systematic literature search

Based on the output of the primary systematic literature search and expert opinion an additional systematic literature search was performed on 29 January 2024 for specific indications for betahistine and cinnarizine with or without dimenhydrinate (see ***Table 1***). The results of this additional systematic literature search are summarised in ***Figure 2***. After subtracting the output from the primary systematic literature search, 30 unique records were retrieved. These records were all excluded during the title and abstract screening.

Figure 2. PRISMA flow diagram of the additional clinical systematic literature search for RCTs



Abbreviations
PRISMA = Preferred Items for Systematic Reviews and Meta-Analyses, RCTs= Randomised controlled trials
Notes
Search date 29 January 2024.

6.2.2 Study characteristics

In the following sections the study characteristics of the included RCTs are reported for the groups betahistine for Ménière's disease (***Section 6.2.2.1***), betahistine for vertigo (***Section 6.2.2.2***), cinnarizine for tinnitus (***Section 6.2.2.3***), and cinnarizine with dimenhydrinate for vertigo (***Section 6.2.2.4***).

6.2.2.1 Betahistine for Ménière's disease

Four RCTs reported data on licensed betahistine use (i.e. 24-48 mg/day) for Ménière's disease (***Table 4***).[39–42] Data on off-label high-dose betahistine use (i.e. 144 mg/day) for Ménière's disease, reported in the RCTs of Adrion et al 2016 and Albu et al 2016, is described in ***Section 9.4***.[32,36]

Adrion et al 2016 studied the efficacy and safety of betahistine in patients aged 18-80 years with unilateral or bilateral Ménière's disease and 2 or more vertigo attacks per month in at least 3 consecutive months before enrolment.[39] Ménière's disease was diagnosed according to the AAO-HNS 1995 criteria and other central or peripheral vestibular disorders such as vestibular migraine were excluded. A history of migraine ≤5 years before enrolment was reported in 18% of the participants. Details on co-medication were not reported. The parallel-design multicentre RCT (BEMED trial) was conducted in Germany from March 2008 to November 2013 and funded by non-industry. Participants were randomised in a 1:1:1 ratio to 9 months low-dose betahistine treatment of 48 mg/day (n=73, mean age 56.1±11.1 years, 53% male), high-dose betahistine of 144 mg/day (n=74), or placebo (n=74, mean age 54.5±12.8 years, 47% male). Baseline characteristics were well balanced between the betahistine and placebo arm.

Liu et al 2020 evaluated the effect of betahistine on quality of life and fall risk (outcome out of scope) in patients with Ménière's disease accompanied by dizziness and imbalance.[40] Ménière's disease was diagnosed according to the AAO-HNS 1995 criteria while excluding other diseases, such as middle-ear diseases. Comorbidities or comedication were not reported in the article. The parallel-design RCT was conducted in China, based on the author affiliation, and funded by non-industry. The number of study centres and study period was not reported. Participants were randomised in a 1:1:1 ratio to 1-month betahistine treatment of 36 mg/day (n=22, mean age 53.3±14.1 years, 43% male), vestibular rehabilitation (n=22, study arm out of scope), or no treatment (n=22, mean age 52.0±15.3 years, 45% male). Baseline characteristics were well balanced between the study arms.

Mira et al 2003 studied the efficacy and safety of betahistine in patients aged 18-65 years with recurrent vertigo resulting from Ménière's disease (n=81 participants; diagnosed according to AAO-HNS 1995 criteria) or paroxysmal positional vertigo of probable vascular origin (n=63 participants; indication out of scope).[41] Comorbidities and comedication were not specified for the patients with Ménière's disease. The parallel-design multicentre RCT was conducted in Italy from January 1999 to June 2001 and funded by industry. Participants were randomised to 3 months betahistine

treatment of 32 mg/day (n=41, mean age and sex not reported for Ménière's disease) or placebo (n=40, mean age and sex not reported for Ménière's disease). Participants had to stop with interfering concomitant therapies at least 7 days before the start of the study treatment. Baseline characteristics were well balanced between the combined group of participants with Ménière's disease or paroxysmal positional vertigo in the betahistine arm and the combined group in the placebo arm.

Ricci et al 1987 conducted a small parallel-design RCT on the efficacy of betahistine in 10 outpatients with Ménière's disease in Italy, based on the author affiliation.[42] The number of centres, study period, funding, diagnosis of Ménière's disease, comorbidities and comedication were not reported. Participants were randomised to betahistine treatment of 24 mg/day (n=5, mean age 36.4±2.2 years, 40% male) or placebo (n=5, mean age 37.0±5.4 years, 45% male). The treatment duration varied per participant and was determined in agreement with the 1972 American Academy of Ophthalmology and Otolaryngology criteria as 10 times the average duration of the free interval between the vertigo attacks declared prior to therapy. The mean treatment duration in the betahistine arm was 10.4±1.2 months and in the placebo arm 7.0±1.3 months. The sex distribution between the study arms was not well balanced.

Table 4. Study characteristics – betahistine for Ménière's disease

Reference	Study design; setting Funding	Country Study period	Study population Study arm	Sample size randomised	Age (mean±SD)	Sex (% male)	Comorbidities n (%)	Comedication n (%)	Diagnosis, unilateral or bilateral (definition) Exclusion criteria related to diagnosis	Intervention - brand name - dose - treatment duration
Adrion et al 2016	Parallel RCT; multicentre Non-industry funded	Germany March 2008-Nov 2013	Patients aged 18-80 years with Ménière's disease and ≥2 vertigo attacks/month in ≥3 months before study						Definite Ménière's disease, unilateral or bilateral (AAO-HNS 1995 criteria) Other central or peripheral vestibular disorders, e.g. vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, phobic postural vertigo	Betahistine - Vasomotal - low dose: 48 mg/day (24 mg bid) - *high dose: 144 mg/day (48 mg tid)*[a] - 9 months
			Betahistine low dose	73	56.1±11.1 years	53%	history of migraine: 9 (12%)	NR[b]		
			Betahistine high dose[a]	*74*	*56.1±12.6 years*	*47%*	*history of migraine: 13 (18%)*	*NR*[b]		
			Placebo	74	54.5±12.8 years	47%	history of migraine: 17 (23%)	NR[b]		
Liu et al 2020	Parallel RCT; NR Non-industry funded	China (author affiliation) NR	Patients with Ménière's disease accompanied by dizziness and imbalance						Definite Ménière's disease, NR (AAO-HNS 1995 criteria) Cognitive dysfunction, neuromuscular system disorders, central nervous system or spinal cord defects, middle-ear diseases, or other acute medical conditions	Betahistine - NR - 36 mg/day (12 mg tid) - 1 month
			Betahistine	22[c]	53.3±14.1 years	43%	NR	NR		
			No treatment	22[c]	52.0±15.3 years	45%	NR	NR		
Mira et al 2003	Parallel RCT; multicentre Industry funded	Italy Jan 1999-June 2001	Patients aged 18-65 years with Ménière's disease						Definite Ménière's disease, NR (AAO-HNS 1995 criteria) Concomitant infectious and definite cerebrovascular diseases	Betahistine - supplied by Grunenthal-Formenti, Milan - 32 mg/day (16 mg bid) - 3 months
			Betahistine	41	NR (46.9±13.1 years[d])	NR (44%[d])	NR (20%[d])[e]	NR (25%[d])[f]		
			Placebo	40	NR (48.8±14.3 years[d])	NR (39%[d])	NR (13%[d])[e]	NR (16%[d])[f]		
Ricci et al 1987	Parallel RCT; NR NR	Italy (author affiliation) NR	Patients with Ménière's disease						Ménière's disease, NR (definition NR) NR	Betahistine - Microser - 24 mg/day (8 mg tid) - 10.4±1.2 months[h]
			Betahistine	5	36.4±2.2 years	40%	NR	NR[g]		
			Placebo	5	37.0±5.4 years	80%	NR	NR[g]		

Abbreviations
AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery, bid = bis in die (twice a day), ITD = intratympanic dexamethasone, NR = not reported, SD = standard deviation, tid = ter in die (3 times a day).

Notes
a = Data on off-label betahistine use will be described in ***Section 9.4***.
b = The following quote is from Adrion et al 2016 “There were no disallowed concomitant drugs used during the study except for antihistaminic drugs, because we aimed to assess the efficacy of the assigned prophylactic treatment irrespective of rescue medication use by measuring efficacy conditional on real life adherence. Hence, rescue medication for managing of acute vertigo related symptoms such as vomiting or nausea could also be prescribed, because a possible effect on the occurrence of vertigo attacks is unknown.” [39] (page 4)
c = Baseline characteristics reported for n=21 betahistine and n=20 placebo.
d = Baseline characteristics reported for total population of patients with Ménière’s disease or paroxysmal positional vertigo of probable vascular origin: betahistine n=75; placebo n=69.
e = Concomitant disease not further specified.
f = Concomitant use antivertigo drugs, drugs that act on cerebral circulation, antihistamines, calcium antagonists, antiaggregants, thiazide diuretics, corticosteroids and benzodiazepines was not permitted during the study; comedication not further specified.
g = No antivertigo drugs acting on the cerebral circulation, antihistamines and histamine-like drugs were allowed concomitantly.
h = Mean±SD treatment duration varied per patient: 10 times the average duration of the free interval between the vertigo attacks declared prior to therapy in agreement with the 1972 American Academy of Ophthalmology and Otolaryngology criteria. Mean±SD treatment duration placebo: 7.0±1.3 months.

6.2.2.2 Betahistine for vertigo

Three RCTs reported data on licensed betahistine use (i.e. 24-48 mg/day) for diverse vertigo aetiologies (***Table 5***).[33–35] Canty et al 1981 evaluated the efficacy and safety of betahistine in patients aged ≤70 years with episodic rotatory vertigo of peripheral origin for at least one year.[33] The diagnosis of peripheral vertigo without established cause was based on the Kane and Strong 1957 criteria and patients with classical Ménière's disease or central vertigo due to any cause were excluded. Comorbidities or comedication were not reported in the article. The cross-over single centre RCT was conducted in the United Kingdom between October 1974 and June 1976. Funding was not reported. After a wash-out placebo treatment of 4 weeks the participants were randomised to 8 weeks betahistine treatment of 32 mg/day (n=15) or placebo (n=17) for the first period before cross-over. Baseline characteristics between the study arms were comparable based on p-values, but no further data on these characteristics was reported.

Conraux et al 1988 studied the efficacy and safety of betahistine in patients having vertigo attacks for at least 3 months, with ≥6 attacks in 2 months before enrolment and ≥3 attacks during 1 month placebo treatment.[34] Comorbidities or comedication were not reported in the article. The parallel-design multicentre RCT was probably conducted in France and Belgium, based on the author affiliations. The study period and funding were not reported. After one month of wash-out placebo treatment the participants were randomised to 3 months betahistine treatment (n=27 analysed) or placebo (n=20 analysed). The total sample size at baseline was 57; the number of participants randomised to each study arm and the baseline characteristics was not reported. A flexible dose of 3 to 6 betahistine tablets of 8 mg was given to the participants in the intervention arm; according to the authors resulting in a prescribed daily dosage close to 48 mg.

Oosterveld et al 1989 studied the efficacy and safety of betahistine in patients aged <65 years suffering from paroxysmal vertigo (i.e. with the diagnosis Ménière's disease, benign paroxysmal position vertigo, cervical vertigo, or paroxysmal vertigo of undetermined origin), with at least 2 vertigo attacks in the month before enrolment.[35] Infections of the middle or inner ear, Parkinson's disease, brain tumour, head trauma, epilepsy, multiple sclerosis or ocular diseases were excluded. Comorbidities or comedication were not reported in the article. The cross-over multicentre RCT was conducted in the Netherlands, based on the author affiliation. The study period and funding were not reported. Participants were randomised to 5 weeks betahistine treatment of 48 mg/day (n=38 analysed, mean age 44±13 years, 45% male) or placebo (n=44 analysed, mean age 46±11 years, 43% male) for the first period before cross-over. The total sample size at baseline was 100; the number of participants randomised to each study arm was not reported. Baseline characteristics were balanced between the study arms.

Table 5. Study characteristics – betahistine for vertigo

Reference	Study design; setting Funding	Country Study period	Study population Study arm	Sample size randomised	Age (mean±SD)	Sex (% male)	Comorbidities n (%)	Comedication n (%)	Diagnosis (definition) Exclusion criteria related to diagnosis	Intervention - brand name - dose - treatment duration
Canty et al 1981	Cross-over RCT[a]; single centre NR	UK Oct 1974-June 1976	Patients aged ≤70 years with episodic rotatory vertigo of peripheral origin for ≥1 year						Peripheral vertigo without established cause (Kane and Strong 1957 criteria) Central vertigo due to any cause; classical Ménière's disease (Hinchcliffe, 1961)	Betahistine - Serc - 32 mg/day (16 mg qd and 8 mg bid) - 8 weeks
			Betahistine	15	NR[b]	NR[b]	NR	NR[c]		
			Placebo	17	NR[b]	NR[b]	NR	NR[c]		
Conraux et al 1988	Parallel RCT; multi-centre NR	France, Belgium (author affiliations) NR	Patients with vertigo attacks for ≥3 months, with ≥6 attacks in 2 months before study and ≥3 attacks during 1 month with wash-out placebo treatment						Chronic vertigo, when it reflected a hallucination of movement of objects in relation to the subject, or vice versa, and involvement of the vestibule (definition NR) NR	Betahistine - Serc - variable dose, close to 48 mg/day - 3 months
			Betahistine	NR[d] (27 analysed)	NR	NR	NR	NR		
			Placebo	NR[d] (20 analysed)	NR	NR	NR	NR		
Oosterveld et al 1989	Cross-over RCT[a]; multi-centre NR	The Netherlands (author affiliation) NR	Patients aged <65 years with paroxysmal vertigo, with ≥2 vertigo attacks in 1 month before study						Paroxysmal vertigo with the diagnosis Ménière's disease (n=37; 45%), benign paroxysmal position vertigo (n=11; 13%), cervical vertigo (n=5; 6%), or paroxysmal vertigo of undetermined origin (n=29; 35%) (definition NR) Infections of middle or inner ear, Parkinson's disease, brain tumour, head trauma, epilepsy, multiple sclerosis or ocular diseases	Betahistine - Betaserc - 48 mg/day (16 mg tid) - 5 weeks
			Betahistine	NR[e] (38 analysed)	44±13 years	45%	NR	NR[f]		
			Placebo	NR[e] (44 analysed)	46±11 years	43%	NR	NR[f]		

Abbreviations
bid = bis in die (twice a day), NR = not reported, qd = quaque die (once a day), SD = standard deviation, tid = ter in die (3 times a day), UK = United Kingdom.
Notes
a = Prior cross-over data extracted.
b = No significant difference in age and sex between study arms; total population aged between 26-62 years and 59% male.
c = No statistically significant difference in concurrent medication for other diseases (p=1.00); no phenothiazines, antihistamines or other antivertigo drugs were allowed concomitantly.
d = Total sample size at baseline n=57.
e = Total sample size at baseline n=100.
f = No antihistamines, phenothiazines, vasodilators, barbiturates or tranquillizers were allowed concomitantly.

6.2.2.3 Cinnarizine for tinnitus

One RCT reported data on licensed cinnarizine use (i.e. 75 mg/day) for tinnitus (***Table 6***).[36] Podoshin et al 1991 studied the effect of 3 treatment modalities on idiopathic subjective tinnitus.[36] The diagnosis of idiopathic subjective tinnitus was not defined, clear pathologies such as Ménière's disease, acoustic neurinoma and cochlear otosclerosis were excluded. Comorbidities or comedication were not reported in the article. The parallel-design RCT was conducted in Israel, based on the author affiliation. The number of centres, study period and funding were not reported. Participants were randomised to 10 weeks cinnarizine treatment of 75 mg/day (n=10, mean age 56 years, 70% male), acupuncture (n=10, study arm out of scope), biofeedback (n=10, study arm out of scope), placebo to cinnarizine (n=20, mean age 59 years, 50% male), or placebo to biofeedback (n=10, study arm out of scope). Baseline characteristics were not compared in the article between the study arms.

Table 6. Study characteristics – cinnarizine for tinnitus

Reference	Study design; setting Funding	Country Study period	Study population						Diagnosis (definition) Exclusion criteria related to diagnosis	- intervention - brand name - dose - treatment duration
			Study arm	Sample size randomised	Age (mean ± SD)	Sex (% male)	Comorbidities n (%)	Comedication n (%)		
Podoshin et al 1991	Parallel RCT; NR NR	Israel (author affiliation) NR	Patients with idiopathic subjective tinnitus						Idiopathic subjective tinnitus (NR) Clear pathologies, e.g. Ménière's disease, acoustic neurinoma, cochlear otosclerosis	Cinnarizine - NR - 75 mg/day (25 mg tid) - 10 weeks
			Cinnarizine	10	56±NR years (range 35-67)	70%	NR	NR		
			Placebo	20	59±NR years (range 45-72)	50%	NR	NR		

Abbreviations
NR = not reported, SD = standard deviation, tid = ter in die (3 times a day).

6.2.2.4 Cinnarizine with dimenhydrinate for vertigo

Two RCTs reported data on licensed cinnarizine with dimenhydrinate use (i.e. 60 mg/day of cinnarizine and 120 mg/day of dimenhydrinate) for vertigo (***Table 7***).[37,38] Otto et al 2008 studied the efficacy and safety of 2 treatments in patients suffering from vertigo associated with vertebrobasilar insufficiency and who showed at least 2 of the symptoms: impaired hearing, impaired vision, tinnitus or headache.[37] The diagnosis of vertebrobasilar insufficiency was not defined, vertigo caused by diseases other than vertebrobasilar insufficiency such as cardiovascular diseases were excluded. Comorbidities were reported in 50% of the participants. The parallel-design single centre RCT was conducted in Germany. The study period and funding were not reported. After a washout period of 2 weeks of antivertigo drugs participants were randomised to 4 weeks treatment of 60 mg/day cinnarizine with 120 mg/day dimenhydrinate (n=11, mean age 52.6±9.5 years, 18% male), betahistine (n=13, study arm out of scope), or placebo (n=13, mean age 49.5±12.1 years, 8% male). The

betahistine study arm was out of scope, since this group was compared with cinnarizine with dimenhydrinate and not with placebo. Baseline characteristics were well balanced between the study arms, but the mean vertigo baseline score in the cinnarizine with dimenhydrinate arm was higher than in the placebo arm at a 20% significance level (p=0.093).

Pytel et al 2007 studied the efficacy and safety of 3 treatments in patients aged >30 years with central, peripheral or combined central/peripheral vestibular vertigo, who assessed at least one vertigo symptom as being of medium intensity and who had abnormal vestibulospinal movement patterns on craniocorpography.[38] The diagnosis of vertigo was not defined in detail, vertigo caused by Ménière's disease, benign paroxysmal positional vertigo, areflexia , or vertigo caused by non-vestibular disorders such as psychogenic vertigo were excluded. Examples of central vertigo were vertigo caused by vertebrobasilar ischemia, vascular encephalopathy, basilar impression or cerebral contusion. Examples of peripheral vertigo were vertigo caused by vestibular neuropathy, labyrinthitis or labyrinth contusion. The authors highlight in their discussion section that patients with vestibular vertigo of central, peripheral or central/peripheral origin were included in their study to mirror the "typical" vertigo patient for whom cinnarizine with dimenhydrinate is prescribed by general practitioners, otologists and neurologists. Comorbidities were reported in 61% of the participants. The parallel-design multicentre RCT was conducted in Hungary and funded by industry. The study period was not reported. After a washout period of 7 days of antivertigo agents and/or drugs with cerebrovascular activity participants were randomised to 4 weeks treatment of 60 mg/day cinnarizine with 120 mg/day dimenhydrinate (n=61, 51.3±9.8 years, 33% male), cinnarizine (n=61, study arm out of scope), dimenhydrinate (n=64, study arm out of scope), or placebo (n=60, mean age 49.7±11.2 years, 33% male). The cinnarizine arm and dimenhydrinate arm were out of scope, since no comparisons were made with placebo. Baseline characteristics were well balanced between the study arms.

Table 7. Study characteristics – cinnarizine with dimenhydrinate for vertigo

Reference	Study design; setting Funding	Country Study period	Study population Study arm	Sample size randomised	Age (mean±SD)	Sex (% male)	Comorbidities n (%)	Comedication n (%)	Diagnosis (definition) Exclusion criteria related to diagnosis	Intervention - brand name - dose - treatment duration
Otto et al 2008	Parallel RCT; single centre NR	Germany NR	Patients with vertigo associated with VBI and ≥2 of the symptoms impaired hearing, impaired vision, tinnitus, or headache						VBI (NR) Vertigo caused by diseases other than VBI (e.g. cardiovascular diseases)	Cinnarizine with dimenhydrinate - supplied by Hennig Arzneimittel, Germany - 60 mg/day cinnarizine & 120 mg/day dimenhydrinate (fixed combination of 20 mg cinnarizine & 40 mg dimenhydrinate tid) - 4 weeks
			Cinnarizine with dimenhydrinate	11	52.6±9.5 years	18%	7 (64%)[a]	5 (45%)[b]		
			Placebo	13	49.5±12.1 years	8%	5 (38%)[a]	4 (31%)[b]		
Pytel et al 2007	Parallel RCT; multi-centre Industry funded	Hungary NR	Patients aged >30 years with central, peripheral or combined central/peripheral vestibular vertigo, who assessed ≥1 vertigo symptom as being of medium intensity (≥2 on 5-point VAS) and abnormal vestibulospinal movement patterns on craniocorpography						Central vertigo[e] (NR) e.g. caused by vertebrobasilar ischemia, vascular encephalopathy, basilar impression, cerebral contusion; Peripheral vertigo[e] (NR) e.g. caused by vestibular neuropathy, labyrinthitis, labyrinth contusion; Combined central/peripheral vestibular vertigo[e] (NR) Ménière's disease, benign paroxysmal positional vertigo, bilateral caloric inexcitability (areflexia), vertigo caused by non-vestibular disorders (e.g. psychogenic vertigo)	Cinnarizine with dimenhydrinate - supplied by Hennig Arzneimittel, Germany - 60 mg/day cinnarizine & 120 mg/day dimenhydrinate (fixed combination of 20 mg cinnarizine & 40 mg dimenhydrinate tid) - 4 weeks
			Cinnarizine with dimenhydrinate	61	51.3±9.8 years	33%	40 (66%)[c]	42 (69%)[d]		
			Placebo	60	49.7±11.2 years	33%	34 (57%)[c]	34 (57%)[d]		

Abbreviations
NR = not reported, SD = standard deviation, tid = ter in die (3 times a day), VAS = visual analogue scale, VBI = vertebrobasilar insufficiency.
Notes
a = Also includes patients reporting previous diseases and operations; concomitant disease not further specified.
b = Concomitant use of monoamine oxidase inhibitors or aminoglycoside antibiotics was not permitted during the study; comedication not further specified.
c = Concomitant diseases constituted ~40% of cardiovascular diseases, followed by ~20% disorders of the locomotor apparatus.
d = Concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, parasympatholytics, glucocorticoids, antihistamines or heparin was not permitted during the study; ~40% of concomitant medications were cardiovascular drugs, ~13% were drugs acting on the central nervous system and ~9% were analgesics and antirheumatics.
e =The number of patients in these groups were reported only for the total population, not for the cinnarizine with dimenhydrinate and placebo arm: n=38 (15%) of the randomised patients were diagnosed with peripheral vertigo, n=49 (20%) were diagnosed with central vertigo, n=159 (65%) were diagnosed with combined central/peripheral vertigo.

6.2.3 Quality assessment of included studies

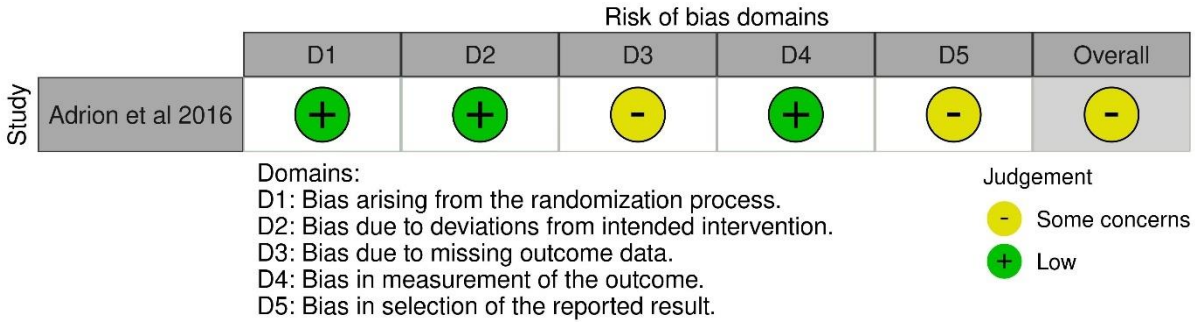
The risk of bias of the included RCTs was assessed with the RoB 2 tool on a per outcome basis for 5 domains, including bias due to the randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result.[26] In the following sections the risk of bias is outlined for the outcomes of interest for the 4 groups betahistine for Ménière's disease (***Section 6.2.3.1***), betahistine for vertigo (***Section 6.2.3.2***), cinnarizine for tinnitus (***Section 6.2.3.2***), and cinnarizine with dimenhydrinate for vertigo (***Section 6.2.3.2***). Summary figures of the risk of bias are enclosed in ***Appendix C.***

6.2.3.1 Betahistine for Ménière's disease

6.2.3.1.1 Outcome vertigo

The overall risk of bias for the outcome vertigo attack frequency reported in the RCT of Adrion et al 2016 was "some concerns" (***Table 8***).[39] Adrion et al 2016 randomised the participants based on an internet-generated block sequence generated by an investigator with no clinical involvement in the trial. The RCT was double-blind; patients, clinicians, core laboratories and trial staff were blinded. A placebo was used as comparator and also the low-dose betahistine arm received placebo pills to align with the number of pills given in the high-dose betahistine arm. It was not highlighted in the article if there were deviations from the intended intervention that arose because of the trial context. Outcome data was reported for 79% (58/73) of the randomised participants in the betahistine arm and 80% (59/74) of the participants in the placebo arm. Reasons for drop-out in the betahistine arm were: withdrawal of informed consent (n=1), lost to follow-up (n=1), adverse events (n=5), lack of efficacy (n=4), lack of compliance (n=1), no diary (n=1), and no time or study duration (n=2). Reasons for drop-out in the placebo arm were: withdrawal of informed consent (n=6), lost to follow-up (n=5), no diary (n=1), and lack of efficacy (n=3). Missing data was accounted for during the analysis using imputation, however this should not be assumed to fully correct for bias due to missing outcome data, and therefore the risk of bias for this domain was rated as "some concerns". The subjective outcome was recorded by participants by daily diary recordings and the individual attack rate was standardised on a 30-day interval. For the outcome vertigo attack frequency pseudobaseline data was used, i.e. data documented during the first treatment month, pretreatment attack data was not available. Data was analysed in accordance with a pre-specified analysis plan. This plan was changed because of the large amount of missing outcome data and data was reported only after 9 months of treatment and not after the further follow-up of 3 months at 12 months.

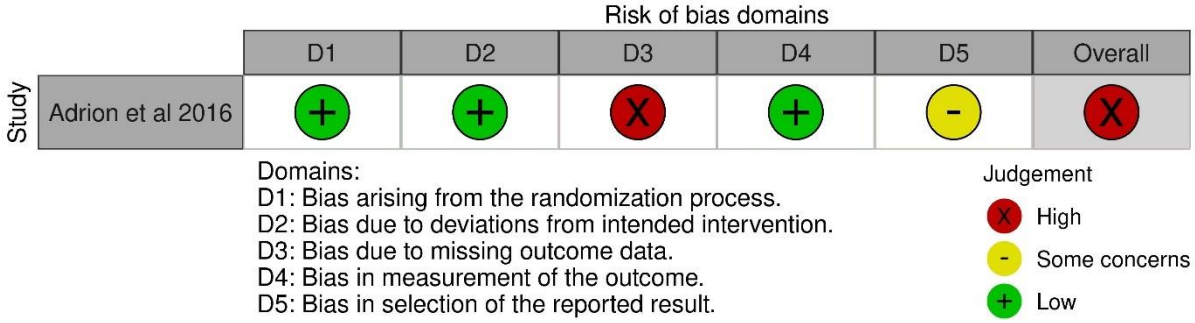
Table 8. Risk of bias of RCT on betahistine for Ménière's disease – vertigo attack frequency



6.2.3.1.2 Outcome tinnitus

The overall risk of bias for the outcome tinnitus intensity reported in the RCT of Adrion et al 2016 was high (***Table 9***).[39] Most risk of bias issues are described above for the outcome vertigo. Outcome data on tinnitus intensity was reported only for 33% (24/73) of the randomised participants in the low-dose betahistine arm and 47% (35/74) of the participants in the placebo arm, resulting in a high risk of bias. Missing data was accounted for during the analysis using imputation, however this should not be assumed to correct for bias due to missing outcome data. Tinnitus intensity was determined with pure tone audiometry, measured during clinic visits.

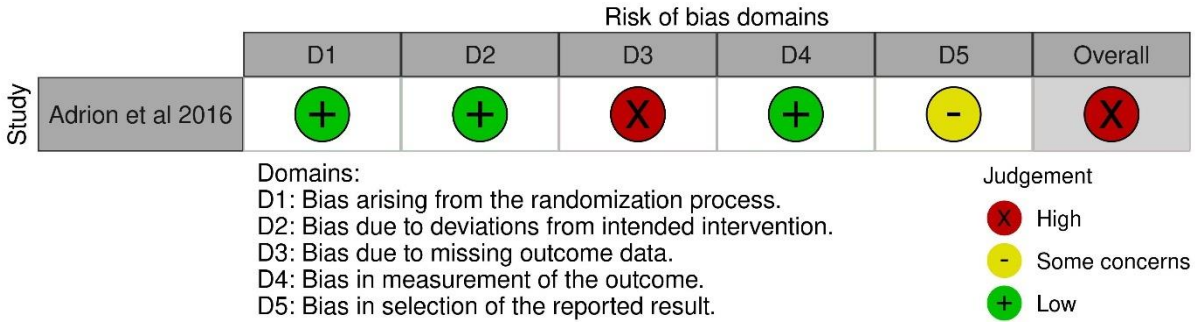
Table 9. Risk of bias of RCT on betahistine for Ménière's disease – tinnitus intensity



6.2.3.1.3 Outcome hearing

The overall risk of bias for the outcome hearing loss reported in the RCT of Adrion et al 2016 was high (***Table 10***).[39] Most risk of bias issues are described above for the outcome vertigo. Outcome data on hearing loss for different frequencies was reported only for 55% (40/73) to 70% (51/73) of the randomised participants in the low-dose betahistine arm and for 46% (34/74) to 64% (47/74) of the participants in the placebo arm, resulting in a high risk of bias. Missing data was accounted for during the analysis using imputation, however this should not be assumed to correct for bias due to missing outcome data. The outcome hearing loss was determined with pure tone audiometry, measured during clinic visits.

Table 10. Risk of bias of RCT on betahistine for Ménière's disease – hearing loss

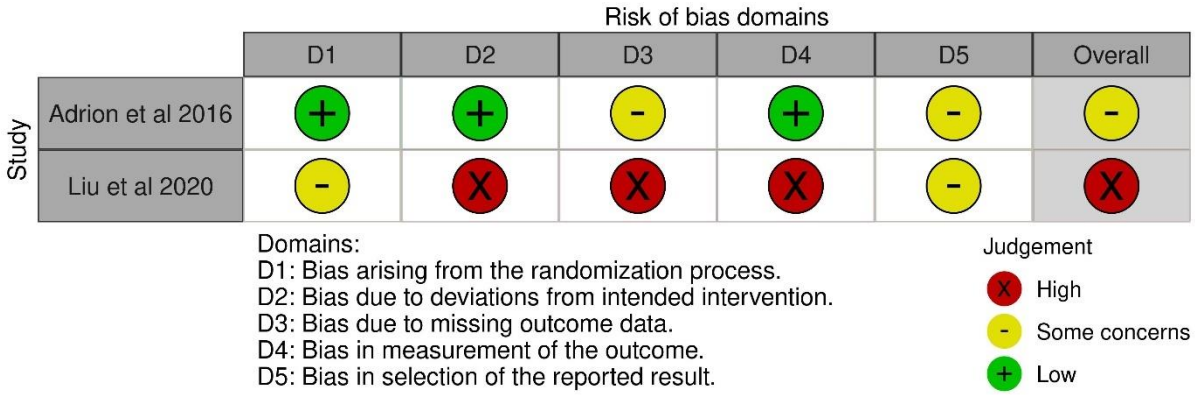


6.2.3.1.4 Outcome health-related quality of life

For the outcome HRQoL assessed with the dizziness handicap inventory (DHI) reported in the RCT of Adrion et al 2016 the overall risk of bias was "some concerns" and high for Liu et al 2020 (***Table 11***).[32,33] Most risk of bias issues for the RCT of Adrion et al 2016 are described above for the outcome vertigo.[39] Outcome data on DHI was reported for 78% (57/73) of the randomised participants in the low-dose betahistine arm and 76% (56/74) of the participants in the placebo arm. Missing data was accounted for during the analysis using imputation, however this should not be assumed to correct for bias due to missing outcome data, and therefore the risk of bias for this domain was rated as "some concerns". HRQoL was measured with the self-administered questionnaire DHI during the clinic visits at baseline and after 9 months of treatment.

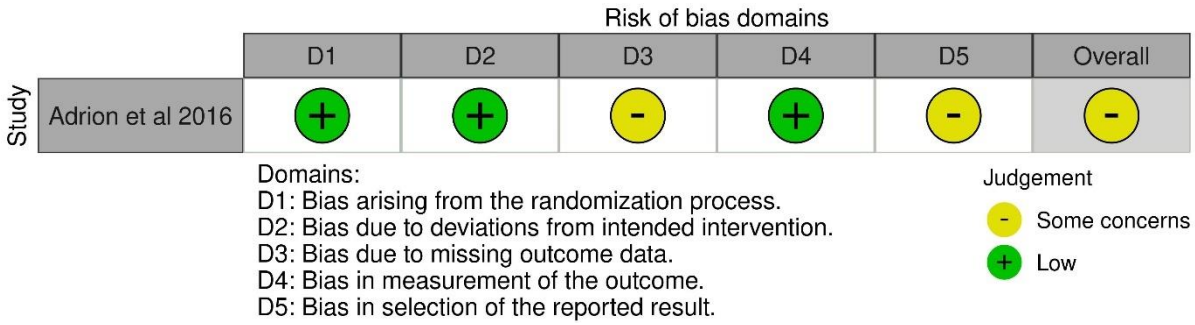
Liu et al 2020 did not report details on the randomisation process and allocation concealment.[40] The comparator was no treatment, because vestibular rehabilitation was studied as third study arm. Blinding was not reported. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Outcome data on DHI was reported for 95% (21/22) of the randomised participants in the betahistine arm and 90% (20/22) of the participants in the placebo arm. These 3 missing participants experienced a vertigo attack and were excluded from the study, which results in a high risk of bias when HRQoL is based on dizziness. HRQoL was measured at baseline and after one month of treatment with the self-administered questionnaire DHI. The lack of placebo as comparator and unclarity of blinding is a high risk of bias for measuring the subjective outcome HRQoL. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 11. Risk of bias of RCTs on betahistine for Ménière's disease – HRQoL assessed with DHI



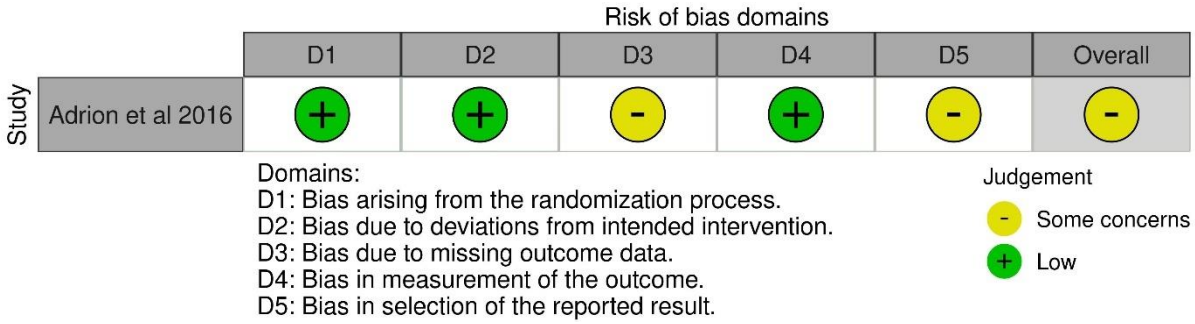
The overall risk of bias for the outcome HRQoL assessed with the vestibular disorders activities of daily living (VDADL), reported in the RCT of Adrion et al 2016 was "some concerns" (***Table 12***).[39] Most risk of bias issues are described above for the outcome vertigo. Outcome data on VDADL was reported for 79% (58/73) of the randomised participants in the low-dose betahistine arm and 77% (57/74) of the participants in the placebo arm. Missing data was accounted for during the analysis using imputation, however this should not be assumed to correct for bias due to missing outcome data, and therefore the risk of bias for this domain was rated as "some concerns". HRQoL was measured with the self-administered questionnaire VDADL during the clinic visits at baseline and after 9 months of treatment.

Table 12. Risk of bias of RCT on betahistine for Ménière's disease – HRQoL assessed with VDADL



The overall risk of bias for the outcome HRQoL assessed with the mini-tinnitus impairment questionnaire score based on 12 items (MiniTF12), reported in the RCT of Adrion et al 2016 was "some concerns" (***Table 13***).[39] Most risk of bias issues are described above for the outcome vertigo. Outcome data on the MiniTF12 was reported for 79% (58/73) of the randomised participants in the low-dose betahistine arm and 73% (54/74) of the participants in the placebo arm. Missing data was accounted for during the analysis using imputation, however this should not be assumed to correct for bias due to missing outcome data, and therefore the risk of bias for this domain was rated as "some concerns". HRQoL was measured with the self-administered questionnaire MiniTF12 during the clinic visits at baseline and after 9 months of treatment.

Table 13. Risk of bias of RCT on betahistine for Ménière's disease – HRQoL assessed with MiniTF12

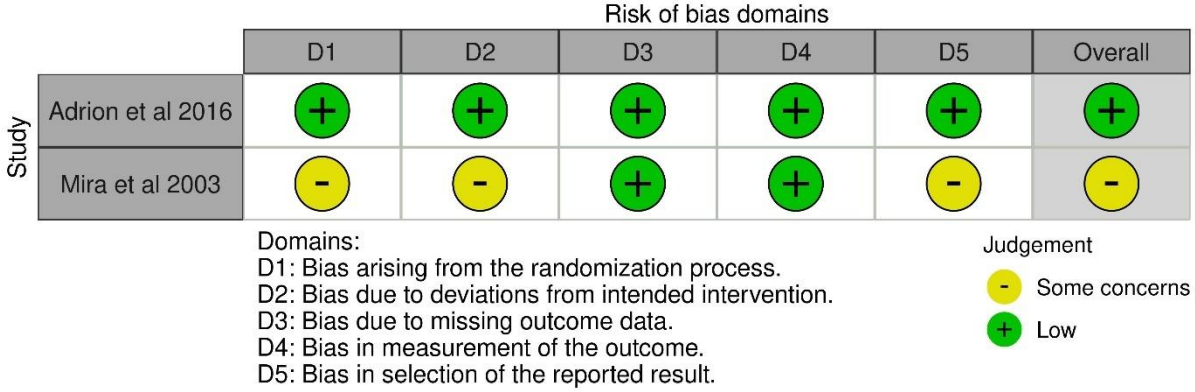


6.2.3.1.5 Outcome serious adverse events

For the outcome serious adverse events reported in the RCT of Adrion et al 2016 the overall risk of bias was low and "some concerns" for Mira et al 2003 (***Table 14***).[32,34] Most risk of bias issues for the RCT of Adrion et al 2016 are described above for the outcome vertigo.[39] Outcome data on serious adverse events was reported for 99% (72/73) of the randomised participants in the low-dose betahistine arm and 100% (74/74) of the participants in the placebo arm. Serious adverse events were assessed at 1, 4, 6 and 9 months from reports of adverse events, laboratory parameters, vital signs, and physical or neurological examinations. Adverse events occurring in the first 3 weeks after cessation of treatment were included.

Mira et al 2003 did not report details on the randomisation process and allocation concealment.[41] The RCT was double-blind (no further details) with a placebo as comparator. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Outcome data on serious adverse was reported for all randomised participants. Details of adverse events assessed were time of onset, type of effect, severity, dose taken, duration of treatment, action taken, outcome of the event, and causal relationship according to the investigator. The risk of bias for the domain measurement of the outcome was low due to the objectivity of the outcome. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 14. Risk of bias of RCT on betahistine for Ménière's disease – SAEs

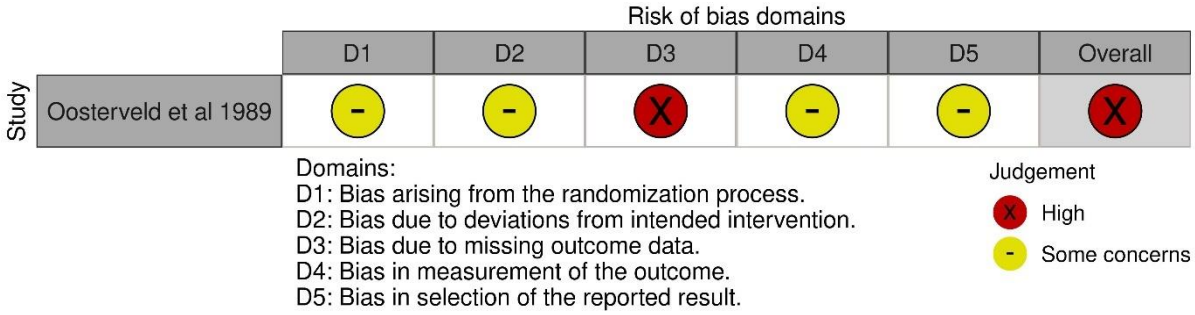


6.2.3.2 Betahistine for vertigo

6.2.3.2.1 Outcome vertigo

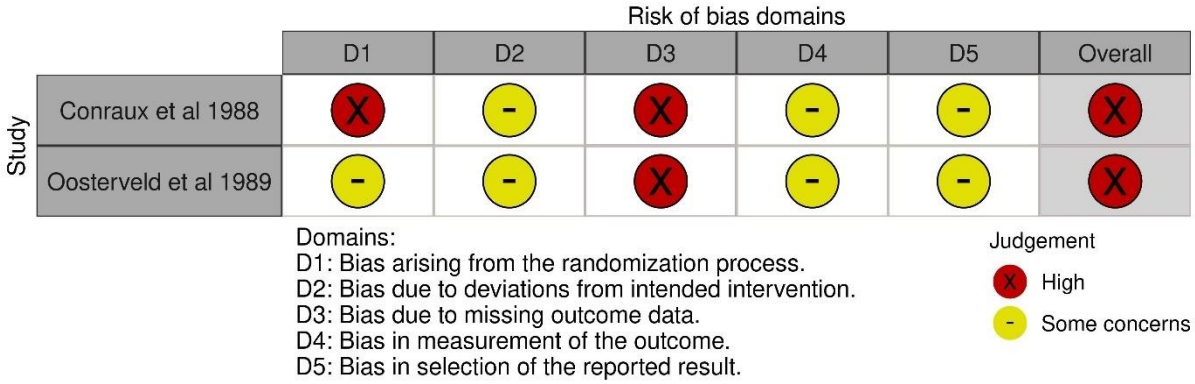
The overall risk of bias for the outcomes vertigo attack frequency and duration reported in the RCT of Oosterveld et al 1989 was high (***Table 15***).[35] Oosterveld et al 1989 did not report details on the randomisation process and allocation concealment. The patient characteristics of the study arms were comparable; however some differences were reported for the pre-treatment values of the outcomes. The RCT was double-blind (no further details) with a placebo as comparator. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Multiple issues resulted in a high risk of bias due to missing outcome data. Outcome data was reported only for 72% (82/114) of the randomised participants. Reasons for withdrawal from treatment, such as side effects, were reported for 6 participants: 4 in the betahistine arm and 2 in the placebo arm. Reasons for exclusion from analysis were not specified per study arm: 14 participants were excluded because of eligibility criteria (i.e. age >65 years, attack frequency <2 per month, concurrent illness), 5 for incompliance, and 7 for missing data. It is unclear why these 14 ineligible participants were excluded from analysis and not excluded before the start of the study. The subjective vertigo outcomes were recorded by participants in diaries when occurring. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 15. Risk of bias of RCT on betahistine for vertigo – vertigo attack frequency and duration



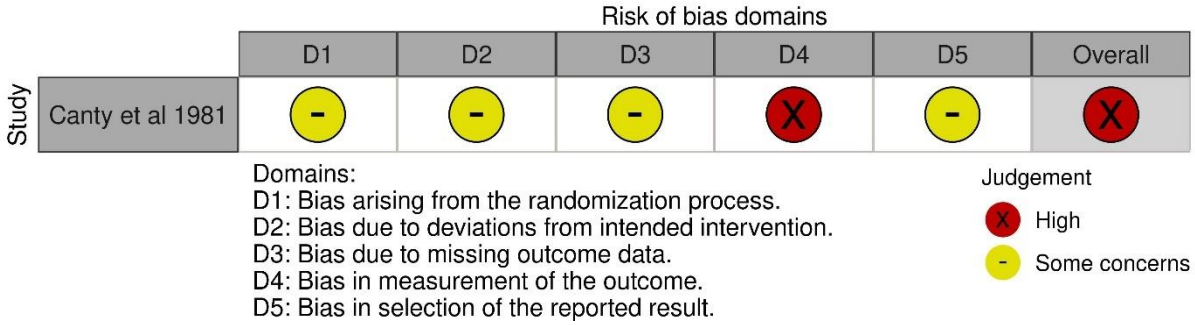
The overall risk of bias for the outcome vertigo attack severity reported in the RCTs of Oosterveld et al 1989 and Conraux et al 1988 was high (***Table 16***).[38,39] The risk of bias issues of Oosterveld et al 1989 are described above. Conraux et al 1988 did not report details on the randomisation process and allocation concealment, nor any baseline characteristics. The RCT was double-blind (no further details) with a placebo as comparator. A flexible dose of 3 to 6 betahistine tablets of 8 mg was given to the participants in the intervention arm; according to the authors resulting in a prescribed daily dosage close to 48 mg. Outcome data was reported for 82% (47/57) of the randomised participants, reasons for missing data were not reported and it was not stated how the missing participants were distributed over the study arms, resulting in a high risk of bias due to missing outcome data. The subjective outcome vertigo attack severity was assessed with a 5-point scale at baseline and after each 4 weeks of treatment. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 16. Risk of bias of RCTs on betahistine for vertigo – vertigo attack severity



The overall risk of bias for the outcome investigator-reported vertigo change reported in the RCT of Canty et al 1981 was high (***Table 17***).[33] Canty et al 1981 did not report details on the randomisation process and allocation concealment. Baseline characteristics between the study arms were comparable based on p-values, but no further data on the baseline characteristics was reported. The RCT was double-blind (no further details) with a placebo as comparator. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Outcome data was reported for 87% (13/15) of the randomised participants in the betahistine arm and 76% (13/17) of the participants in the placebo arm. The investigator-reported vertigo change was based on clinical data recalled by the participants at the end of 8 weeks treatment and some additional clinical information retrieved from the patient forms by retrospective categorisation of unsystemised clinical notes. The subjective outcome vertigo change was not defined. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 17. Risk of bias of RCT on betahistine for vertigo – investigator-reported vertigo change



6.2.3.2.2 Outcome health-related quality of life

For patients with vertigo treated with betahistine no data was reported on the secondary outcome HRQoL.

6.2.3.2.3 Outcome serious adverse events

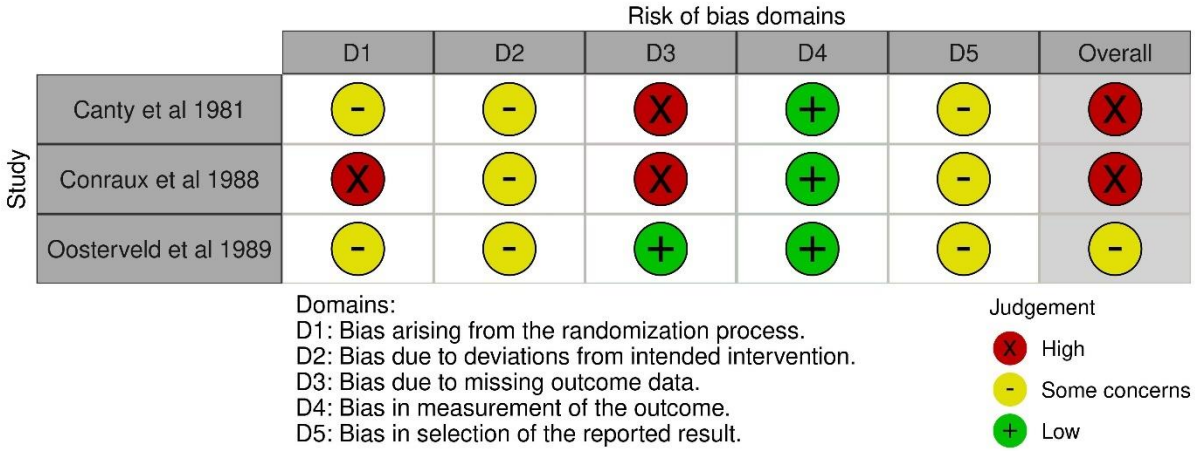
For the outcome serious adverse events reported in the RCTs of Canty et al 1981 and Conraux et al 1988 the overall risk of bias was high, and "some concerns" for Oosterveld et al 1989 (***Table 18***).[33–35]

Most risk of bias issues for the RCT of Canty et al 1981 are described above for the outcome investigator-reported vertigo change.[33] Bias due to missing outcome data was high, because the denominator for the outcome serious adverse events was not reported. Participants were seen at 4-weekly intervals by the investigator who noted any unusual or unwanted signs or symptoms which might represent adverse reactions to the medication during the preceding month. The risk of bias for the domain measurement of the outcome was low due to the objectivity of the outcome.

Most risk of bias issues for the RCT of Conraux et al 1988 are described above for the outcome vertigo attack severity.[34] Bias due to missing outcome data was high, because the denominator for the outcome serious adverse events was not reported. Adverse events were assessed after each month of treatment by variation in clinical values, laboratory examinations, and spontaneous complaints reported by the participant. The risk of bias for the domain measurement of the outcome was low due to the objectivity of the outcome.

Most risk of bias issues for the RCT of Oosterveld et al 1989 are described above for the outcomes vertigo attack frequency and duration.[35] Outcome data for serious adverse events was reported for all randomised participants. Any side effects occurring were recorded in a diary and evaluated after 5 weeks of treatment. The risk of bias for the domain measurement of the outcome was low due to the objectivity of the outcome.

Table 18. Risk of bias of RCTs on betahistine for vertigo – SAEs



6.2.3.3 Cinnarizine for tinnitus

6.2.3.3.1 Outcome tinnitus

The overall risk of bias for the outcomes tinnitus disturbance (***Table 19***) and patient-reported change in tinnitus (***Table 20***) reported in the RCT of Podoshin et al 1991 was high.[36] Podoshin et al 1991 did not report details on the randomisation process and allocation concealment. A placebo was used as comparator, no other information on blinding was reported. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Outcome data was reported for all randomised participants. The subjective tinnitus outcomes were assessed with a questionnaire; however the outcome tinnitus change was not defined. It was not clear whether data was analysed in accordance with a pre-specified analysis plan. It should be noted that Podoshin et al 1991 reported incomplete data on the objective evaluation data of tinnitus; pre-treatment data was not reported and post-treatment data was not compared between the study arms for statistical significance or clinical relevance.

Table 19. Risk of bias of RCT on cinnarizine for tinnitus – tinnitus disturbance

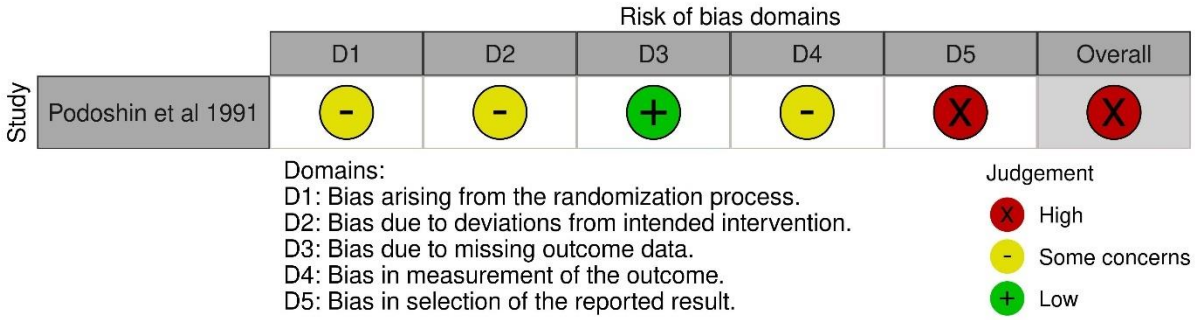
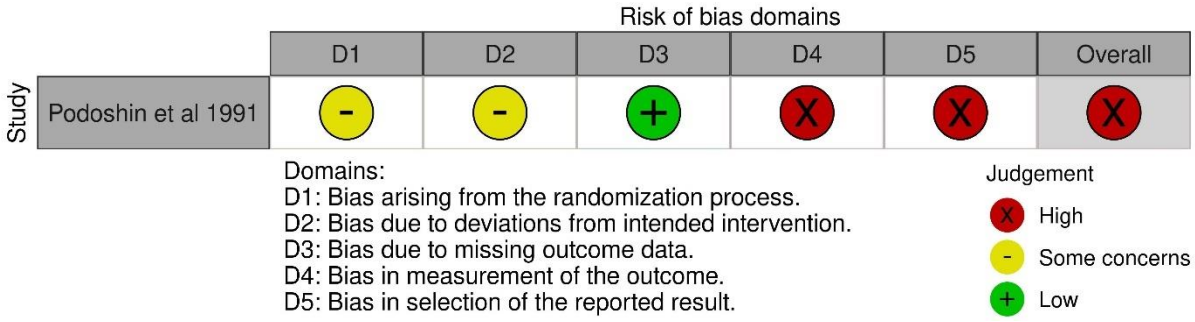


Table 20. Risk of bias of RCT on cinnarizine for tinnitus – patient-reported tinnitus change



6.2.3.3.2 Outcome health-related quality of life

For patients with tinnitus treated with cinnarizine no data was reported on the secondary outcome HRQoL.

6.2.3.3.3 Outcome serious adverse events

For patients with tinnitus treated with cinnarizine no data was reported on the primary outcome serious adverse events.

6.2.3.4 Cinnarizine with dimenhydrinate for vertigo

6.2.3.4.1 Outcome vertigo

The overall risk of bias for the outcomes mean vertigo score (***Table 21***) and patient and investigator-reported overall efficacy of treatment, i.e. vertigo much or very much improved (***Table 22***), reported in the RCTs of Otto et al 2008 and Pytel et al 2007 was "some concerns".[37,38] In both RCTs participants were randomised based on a computer-generated block sequence and no details were reported on the allocation concealment. Both RCTs were double-blind (no further details reported by Otto et al 2008; Pytel et al 2007 reported data cleaning was completed before unblinding) with a placebo as comparator. No information was provided if there were deviations from the intended intervention that arose because of the trial context. The RCT of Otto et al 2007 had to be terminated prematurely due to organisational and technical changes at the ear, nose and throat clinic. At that time 11 participants in the cinnarizine with dimenhydrinate arm and 13 participants in the placebo arm completed the study, instead of the initially planned 20 participants per arm. Outcome data was reported for 100% (11/11) of the randomised participants in the cinnarizine with dimenhydrinate arm and 85% (11/13; drop-out reasons unknown) of the participants in the placebo arm. For Pytel et al 2008 these rates were respectively 100% (61/61) and 97% (58/60; drop-out due to adverse events) for the outcome mean vertigo score and 97% (59/61; drop-out due to adverse events and 'other') and 95% (57/60; drop-out due to adverse events) for the outcome overall efficacy of treatment. The subjective outcome mean vertigo score was assessed with a questionnaire and the subjective outcome patient and investigator-reported overall efficacy of treatment with a verbal rating scale, both assessed during clinic visits. It was not clear whether data was analysed in accordance with a pre-specified analysis plan.

Table 21. Risk of bias of RCTs on cinnarizine with dimenhydrinate for vertigo – mean vertigo score

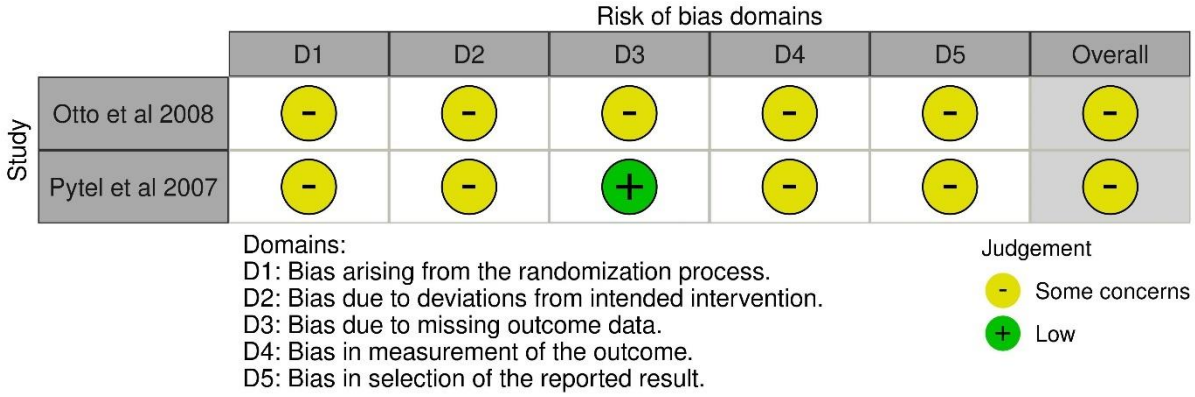
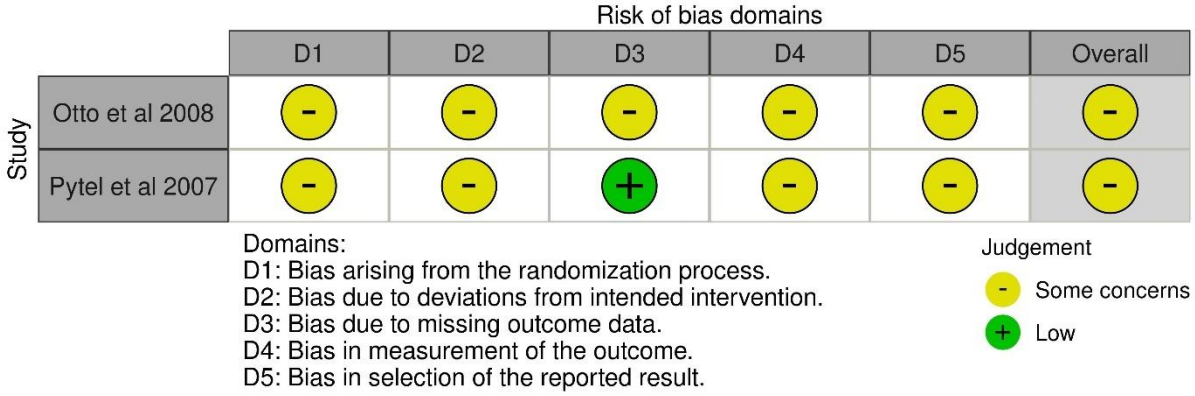


Table 22. Risk of bias of RCT on cinnarizine with dimenhydrinate for vertigo – patient and investigator-reported overall efficacy of treatment



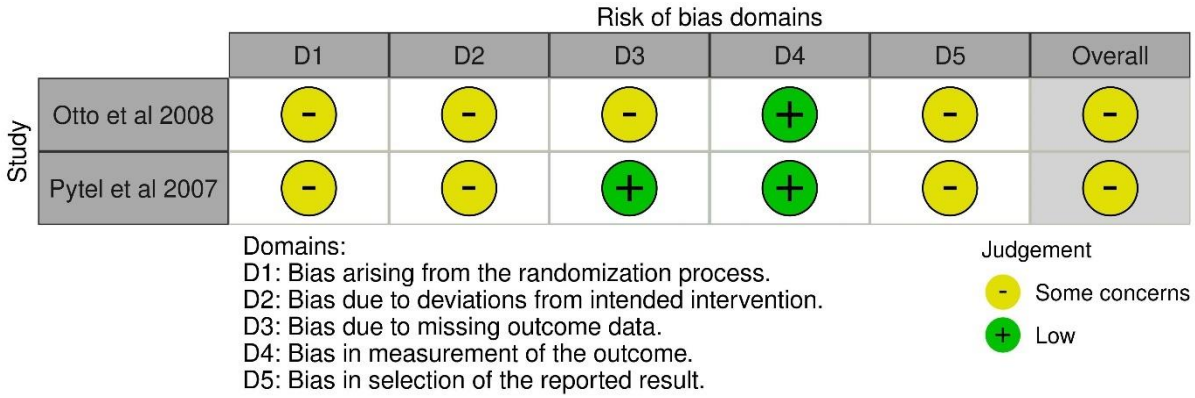
6.2.3.4.2 Outcome health-related quality of life

For patients with vertigo treated with cinnarizine with dimenhydrinate no data was reported on the secondary outcome HRQoL.

6.2.3.4.3 Outcome serious adverse events

The overall risk of bias for the outcome serious adverse events reported in the RCTs of Otto et al 2008 and Pytel et al 2007 was “some concerns” (***Table 23***).[37,38] Most risk of bias issues are described above for the vertigo outcomes. In both RCTs outcome data on serious adverse events was reported for all randomised participants. Otto et al 2008 registered the details of adverse reactions at each visit. The events were reported spontaneously by the patients, observed by the investigator, or reported by the patients in response to general questioning by the investigator. In the RCT of Pytel et al 2007 the incidence, severity and relationship to study treatment of all observed or reported adverse events were recorded by the investigator. The risk of bias for the domain measurement of the outcome was low due to the objectivity of the outcome.

Table 23. Risk of bias of RCT on cinnarizine with dimenhydrinate for vertigo – SAEs



6.2.4 Overview findings

Table 24. Overview findings

	Efficacy					Effective-ness	Safety	
	Vertigo	**Tinnitus**	**Hearing loss**	**Disease-specific HRQoL**	**HRQoL**		**Serious adverse events**	**Other adverse events**
Betahistine for Ménière's disease								
Adrion et al 2016	+ - ol	+ ol	+ ol	+ ol	NR	NA	+	NR
Albu et al 2016	ol	ol	ol	ol	NR	NA	ol	ol
Liu et al 2020	NR	NR	NR	±	NR	NA	NR	NR
Mira et al 2003	-	NR	NR	-	NR	NA	+	+
Ricci et al 1987	-	NR	-	NR	NR	NA	NR	NR
Betahistine for vertigo								
Canty et al 1981	+	NA	NA	NR	NR	NA	?	NR
Conraux et al 1988	± -	NA	NA	NR	NR	NA	?	+
Oosterveld et al 1989	±	NA	NA	NR	NR	NA	?	NR
Cinnarizine for tinnitus								
Podoshin et al 1991	NA	+ ± -	NA	NR	NR	NA	NR	NR
Cinnarizine with dimenhydrinate for vertigo								
Otto et al 2008	+ ±	NA	NA	NR	NR	NA	?	+
Pytel et al 2007	+ ±	NA	NA	NR	NR	NA	?	+

Notes
+ = Relevant data were reported, including effect size with 95% confidence interval and/or p-value or reporting raw data to calculate an effect size with 95% confidence interval.
± = Relevant data were reported, however without reporting the effect size with 95% confidence interval and/or p-value or without reporting raw data to calculate an effect size with 95% confidence interval.
- = Relevant data missing for valid data interpretation; extracted results with missing data were not included in the data synthesis and reported in ***Appendix D.***
? = Effect size with 95% confidence interval not estimable (i.e. zero cases).
ol = Off-label drug use; extracted results on off-label use on the medications of interest were not included in the data synthesis and reported in ***Chapter 9 Additional issues*** and ***Appendix E.***
NA = Not applicable.
NR = Not reported.

6.2.5 Findings efficacy

The findings on the efficacy outcomes of interest for the 4 groups are reported in subsequent sections betahistine for Ménière's disease (***Section 6.2.4.1***), betahistine for vertigo (***Section 6.2.4.2***), cinnarizine for tinnitus (***Section 6.2.4.3***), and cinnarizine with dimenhydrinate for vertigo (***Section 6.2.4.4***).

6.2.5.1 Betahistine for Ménière's disease

For patients with Ménière's disease treated with betahistine the primary efficacy outcomes of interest were vertigo, tinnitus and hearing. Results reported on outcomes with relevant data missing for valid data interpretation (i.e. missing results for a study arm or missing pre-treatment data) were extracted from 3 studies and enclosed in ***Appendix D***; this data was not included in the data synthesis.[32,34,35]

Data on off-label betahistine use for Ménière's disease reported in the RCTs of Adrion et al 2016 and Albu et al 2016 is described in ***Section 9.4***.[32,36]

6.2.5.1.1 Outcome vertigo

During 9 months of placebo treatment the mean vertigo attack rate was significantly lowered by the factor 0.76 (95% CI 0.71 to 0.82) per month in the RCT of Adrion et al 2016 (***Table 25***).[39] The corresponding estimated factor for low-dose betahistine, representing a rate ratio compared with placebo, was not statistically significant (adjusted rate ratio 1.04 [95% CI 0.94 to 1.14]*;* moderate certainty evidence; ***Table 45***). Also during months 7 to 9 of the RCT, during which a prespecified maximal effect of betahistine was assumed, no significant difference between low-dose betahistine and placebo was found (adjusted rate ratio 0.85 [95% CI 0.47 to 1.53]).

Table 25. Efficacy results on betahistine in patients with Ménière's disease – vertigo attack frequency

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD number attacks per month	p-value between group	Post-treatment months 7-9[a] mean (95% CI) number attacks per month	p-value between group	Adjusted monthly decay rate (95% CI) attacks over 9 months	Adjusted rate ratio (95% CI) over 9 months versus placebo	p-value between group	Adjusted rate ratio (95% CI) months 7-9[a] versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	NR[b]	5.8±4.6[b]	0.625	3.20 (1.35 to 7.93)	NR	NR	1.04 (0.94 to 1.14)	0.759	0.85 (0.47 to 1.53)	0.850
	Betahistine high dose (144 mg/day; 9 months)	*NR[b]*	*5.1±4.5[b]*		*3.26 (1.69 to 7.27)*		*NR*	*1.01 (0.92 to 1.11)*		*0.89 (0.49 to 1.63)*	
	Placebo (9 months)	NR[b]	6.2±6.9[b]		2.72 (1.30 to 6.31)		0.76 (0.71 to 0.82)	NA		NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = Assumption of a maximal effect of intervention during the prespecified 90-day assessment period (months 7-9).
b = Pseudobaseline data reported for n=69 betahistine low dose, n=69 betahistine high dose and n=66 placebo. Pseudobaseline data is data documented during the first treatment month (with day 1 being the day of first study drug intake); pre-treatment attack data was not available.
Data on off-label betahistine use will be described in ***Section 9.4***.

6.2.5.1.2 Outcome tinnitus

Adrion et al 2016 assessed the outcome tinnitus intensity with pure tone audiometry.[39] With pure tone audiometry a decrease in dB corresponds to less tinnitus, although the observed changes in this study are very small. After 9 months of treatment no statistically significant adjusted treatment difference (+1.40 dB [95% CI -5.10 to 7.90]) was found between low-dose betahistine and placebo (***Table 26***; low certainty evidence; ***Table 45***).

Table 26. Efficacy results on betahistine for Ménière's disease – tinnitus intensity

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo (dB)	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	24	44.5±22.8[b]	NR	+7.07 (0.53 to 13.60)	0.107	NR	+1.40 (-5.10 to 7.90)	0.338
	Betahistine high dose (144 mg/day; 9 months)	*28*	*54.0±19.8[b]*		*-1.82 (-7.96 to 4.31)*		*NR*	*-3.34 (-9.74 to 3.06)*	
	Placebo (9 months)	35	42.8±22.0[b]		-0.56 (-6.02 to 4.91)		+6.82 (-0.34 to 13.99)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
b = Pre-treatment tinnitus intensity reported for n=40 betahistine low dose, n=45 betahistine high dose and n=50 placebo.
Data on off-label betahistine use will be described in ***Section 9.4***.

6.2.5.1.3 Outcome hearing

Adrion et al 2016 did not find statistically significant adjusted differences between 9 months of low-dose betahistine and placebo treatment for the outcome hearing loss as measured with pure tone audiometry at 4 different frequencies. With pure tone audiometry a decrease in dB corresponds to less hearing loss, although the observed changes in this study are very small. The adjusted treatment difference between low-dose betahistine and placebo across the frequencies evaluated ranged between +0.33 dB (95% CI -3.13 to 3.79) at 250 Hz and +2.83 dB (95% CI -1.93 to 7.59) at 1000 Hz (***Table 27***; ***Table 27 continued***.*;* low certainty evidence; ***Table 45***).[39]

Table 27. Efficacy results on betahistine for Ménière's disease – hearing loss

Reference	Intervention (dose; duration)	Sample size analysed	Hearing loss, pure tone audiometry (PTA) 250 Hz							Hearing loss, pure tone audiometry (PTA) 500 Hz						
	Comparator (duration)		Pre-treatment mean±SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo in (dB)	p-value between group	Pre-treatment mean±SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo (dB)	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	40[b]; 46[c]	32.8±16.0[d]	NR	-1.99 (-5.20 to 1.22)	0.316	NR	+0.33 (-3.13 to 3.79)	0.954	36.5±19.2[e]	NR	+0.29 (-3.64 to 4.21)	0.231	NR	+1.99 (-2.64 to 6.62)	0.597
	Betahistine high dose (144 mg/day; 9 months)	*39[b]; 48[c]*	*29.6±16.0[d]*		*-2.88 (-6.12 to 0.35)*		*NR*	*-0.21 (-3.86 to 3.43)*		*35.4±19.9[e]*		*-3.27 (-7.10 to 0.56)*		*NR*	*-0.08 (-4.51 to 4.35)*	
	Placebo (9 months)	34[b]; 44[c]	29.4±18.2[d]		-5.53 (-9.01 to -2.06)		+4.75 (1.04 to 8.45)	NA		33.6±20.0[e]		-4.37 (-8.39 to -0.36)		+4.94 (0.41 to 9.47)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, PTA = pure tone audiometry, SD = standard deviation.
Notes
a = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
b = Sample size analysed for PTA 250 Hz.
c = Sample size analysed for PTA 500 Hz.
d = Pre-treatment PTA 250 Hz reported for n=51 betahistine low dose, n=55 betahistine high dose and n=54 placebo.
e = Pre-treatment PTA 500 Hz reported for n=58 betahistine low dose, n=64 betahistine high dose and n=60 placebo.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 27 continued. Efficacy results on betahistine for Ménière's disease – hearing loss

Reference	Intervention (dose; duration)	Sample size analysed	Hearing loss, pure tone audiometry (PTA) 1000 Hz							Hearing loss, pure tone audiometry (PTA) 2000 Hz						
	Comparator (duration)		Pre-treatment mean± SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo in (dB)	p-value between group	Pre-treatment mean± SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo (dB)	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	49[b]; 51[c]	37.6±19.7[d]	NR	-0.60 (-4.29 to 3.09)	0.196	NR	+2.83 (-1.93 to 7.59)	0.474	38.7±19.3[e]	NR	+0.61 (-2.58 to 3.80)	0.513	NR	+1.67 (-2.41 to 5.74)	0.504
	Betahistine high dose (144 mg/day; 9 months)	*48[b]; 49[c]*	*34.4±21.3[d]*		*-2.96 (-6.68 to 0.77)*		*NR*	*+1.15 (-3.27 to 5.56)*		*37.9±18.5[e]*		*-1.84 (-5.10 to 1.42)*		*NR*	*-0.68 (-4.75 to 3.39)*	
	Placebo (9 months)	47[b]; 45[c]	35.3±20.7[d]		-5.44 (-9.21 to -1.68)		+4.34 (-0.34 to 9.01)	NA		35.8±19.9[e]		-1.53 (-4.94 to 1.87)		+5.48 (1.30 to 9.66)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, PTA = pure tone audiometry, SD = standard deviation.
Notes
a = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
b = Sample size analysed for PTA 1000 Hz.
c = Sample size analysed for PTA 2000 Hz.
d = Pre-treatment PTA 1000 Hz reported for n=65 betahistine low dose, n=65 betahistine high dose and n=63 placebo.
e = Pre-treatment PTA 2000 Hz reported for n=65 betahistine low dose, n=64 betahistine high dose and n=62 placebo.
*Data on off-label betahistine use will be described in **Section 9.4**.*

6.2.5.1.4 Outcome health-related quality of life

Disease-specific HRQoL assessed with the dizziness handicap inventory (DHI) estimates the impact of dizziness on emotional, functional and physical subdomains. The total score ranges from 0 (best) to 100 (worst). After 9 months of treatment Adrion et al 2016 reported no statistically significant adjusted treatment difference (+0.08 [95% CI -0.17 to 0.33]) between low-dose betahistine and placebo treatment, when averaging the number of available answers with a score range of 0 to 4 per answer (***Table 28****;* moderate certainty evidence; ***Table 45***).[39]

After one month of treatment Liu et al 2020 reported a statistically significant better improvement in DHI in the betahistine arm (calculated treatment change -6.9) compared to the no treatment arm (calculated treatment change -0.8), on a mean total score range of 0 to 100 (***Table 28 continued***; very low certainty evidence; ***Table 45***).[40]

Table 28. Efficacy results on betahistine for Ménière's disease – HRQoL assessed with DHI

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Dizziness handicap inventory (DHI)[a] mean total score, averaging the number of available answers Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	57	1.78±1.01[c]	NR	-0.36 (-0.55 to -0.17)	0.482	NR	+0.08 (-0.17 to 0.33)	0.666
	Betahistine high dose (144 mg/day; 9 months)	*57*	*1.77±0.91[c]*		*-0.52 (-0.71 to -0.33)*		*NR*	*-0.03 (-0.27 to 0.22)*	
	Placebo (9 months)	56	1.69±0.90[c]		-0.50 (-0.69 to -0.31)		-0.10 (-0.35 to 0.15)	NA	

Abbreviations
CI = confidence interval, DHI = dizziness handicap inventory, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = DHI comprises 25 items and assesses the impact of dizziness on emotional (9 items), functional (9 items), and physical (7 items) subdomains. There are 3 answers to each question: "yes" (=4 points), "sometimes" (=2 points), and "no" (=0 points). Total score ranges from 0 to 100; higher score is worse.
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment DHI reported for n=68 betahistine low dose, n=74 betahistine high dose and n=72 placebo.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table28 continued. Efficacy results on betahistine for Ménière's disease – HRQoL assessed with DHI

Reference	Intervention (dose; duration)	Sample size analysed	Dizziness handicap inventory (DHI)[a] mean total score						
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Post-treatment mean±SD	p-value between group	p-value within-group	Calculated mean absolute change ±SD	Calculated treatment difference (95% CI)
Liu et al 2020	Betahistine (36 mg/day; 1 month)	21	39.1±13.5	NR	32.2±11.2	0.019	<0.001	-6.9±NR	-6.1 (NR)
	No treatment (1 month)	20	41.3±13.7		40.5±11.7		0.176	-0.8±NR	

Abbreviations
CI = confidence interval, DHI = dizziness handicap inventory, NR = not reported, SD = standard deviation.
Notes
a = DHI comprises 25 items and assesses the impact of dizziness on emotional (9 items), functional (9 items), and physical (7 items) subdomains. There are 3 answers to each question: "yes" (=4 points), "sometimes" (=2 points), and "no" (=0 points). Total score ranges from 0 to 100; higher score is worse.

Disease-specific HRQoL assessed with the vestibular disorders activities of daily living (VDADL) questionnaire estimates subjects' comfort and ability to perform activities. The total score ranges from 1 (best) to 10 (worst). Adrion et al 2016 did not find a statistically significant adjusted treatment difference (-0.05 [95% CI -0.32 to 0.22]) between low-dose betahistine and placebo treatment after 9 months (***Table 29****;* moderate certainty evidence; ***Table 45***).[39]

Table 29. Efficacy results on betahistine for Ménière's disease – HRQoL assessed with VDADL

Reference	Intervention (dose; duration)	Sample size analysed	Vestibular disorders activities of daily living (VDADL)[a] total score, averaging the number of available answers						
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	58	1.75±1.53[c]	NR	-0.26 (-0.46 to -0.06)	0.547	NR	-0.05 (-0.32 to 0.22)	0.883
	Betahistine high dose (144 mg/day; 9 months)	*58*	*1.78±1.07[c]*		*-0.36 (-0.56 to -0.16)*		*NR*	*-0.06 (-0.33 to 0.20)*	
	Placebo (9 months)	57	1.77±1.35[c]		-0.20 (-0.41 to 0.00)		+0.79 (0.53 to 1.06)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, SD = standard deviation, VDADL = vestibular disorders activities of daily living.
Notes
a = VDADL consists of 28 questions that assess subjects' comfort and ability to perform activities categorised as functional (F), ambulatory (A) and instrumental (I), and a total scale that summarises all 3 categories. Subjects score their responses to each question using integer numbers ranging from 1 (best) to 10 (worst).
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment VDADL reported for n=69 betahistine low dose, n=74 betahistine high dose and n=73 placebo.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Disease-specific HRQoL assessed with the mini-tinnitus impairment questionnaire (MiniTF12) includes most central and characteristic aspects of the full tinnitus questionnaire. The total score

ranges from 0 (best) to 24 (worst). After 9 months Adrion et al 2016 did not find a statistically significant adjusted treatment difference (-0.007 [95% CI -0.14 to 0.13]) between low-dose betahistine and placebo treatment (***Table 30****;* moderate certainty evidence; ***Table 45***).[39]

Table 30. Efficacy results on betahistine for Ménière's disease – HRQoL assessed with MiniTF12

Reference	Intervention (dose; duration)	Sample size analysed	Mini-tinnitus impairment questionnaire (MiniTF12)[a] mean total score, averaging the number of available answers						
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	58	0.81±0.53[c]	NR	-0.11 (-0.21 to -0.01)	0.929	NR	-0.007 (-0.14 to 0.13)	0.97
	Betahistine high dose (144 mg/day; 9 months)	*56*	*0.73±0.48[c]*		*-0.14 (-0.24 to -0.04)*		*NR*	*-0.016 (-0.15 to 0.11)*	
	Placebo (9 months)	54	0.77±0.56[c]		-0.12 (-0.22 to -0.02)		+0.07 (-0.05 to 0.18)	NA	

Abbreviations
CI = confidence interval, MiniTF12 = mini-tinnitus impairment questionnaire, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = MiniTF12 contains selected 12 items from the full tinnitus questionnaire, which reflect most central and characteristic aspects: 5. I am aware of the noises from the moment I get up to the moment I sleep; 16. Because of the noises I worry that there is something seriously wrong with my body; 17. If the noises continue my life will not be worth living; 24. I am more irritable with my family and friends because of the noises; 28. I worry that the noises might damage my physical health; 34. I find it harder to relax because of the noises; 35. My noises are often so bad that I cannot ignore them; 36. It takes me longer to get sleep because of the noises; 39. I am more liable to feel low because of the noises; 43. I often think about whether the noises will ever go away; 47. I am a victim of my noises; 48. The noises have affected my concentration. Each item can be answered as either "true" (=2 points), "partly true" (=1 point) or "not true" (=0 points). Total score ranges from 0 to 24; higher score is worse.
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment MiniTF12 reported for n=69 betahistine low dose, n=74 betahistine high dose and n=72 placebo.
Data on off-label betahistine use will be described in ***Section 9.4****.*

6.2.5.2 Betahistine for vertigo

For patients with vertigo treated with betahistine the primary efficacy outcome of interest was vertigo. Results reported on outcomes with relevant data missing for valid data interpretation (i.e. missing pre-treatment data) were extracted from one study and enclosed in ***Appendix D***; this data was not included in the data synthesis.[34]

6.2.5.2.1 Outcome vertigo

The results of Oosterveld et al 1989 were lacking and seem not consistent for 3 different vertigo outcomes.[35] No effect sizes or between-group p-values were reported. Compared to baseline, after 5 weeks of betahistine treatment a statistically significant decrease was reported in vertigo attack frequency (***Table 31***) and vertigo attack severity (***Table 33***) versus a non-significant decrease for placebo. An opposite result was found for the outcome vertigo attack duration with a non-significant decrease in the betahistine arm and a statistically significant decrease in the placebo arm,

compared to baseline (***Table 32***). Conraux et al 1988 reported a statistically significant difference in vertigo attack severity in favour of betahistine versus placebo after 3 months of treatment, the baseline vertigo attack severity in the betahistine and placebo arm was comparable (***Table 33***).[34] The certainty of the evidence for these outcomes was very low (***Table 46***).

Table 31. Efficacy results on betahistine for vertigo – vertigo attack frequency

Reference	Intervention (dose; duration)	Sample size analysed	Vertigo attack frequency per week				Vertigo attack frequency score per week			
	Comparator (duration)		Pre-treatment n (%) patients	Post-treatment n (%) patients	p-value within group	p-value between group	Pre-treatment mean± SD score[a]	p-value between group	Post-treatment mean± SD score[a]	p-value between group
Oosterveld et al 1989	Betahistine (48 mg/day ; 5 weeks)	38	0: 0 (0%) <1: 1 (3%) 1: 10 (26%) 2-3: 9 (24%) 4-6: 3 (8%) 7-10: 6 (16%) >10: 9 (24%)	0: 4 (11%) <1: 11 (29%) 1: 7 (18%) 2-3: 6 (16%) 4-6: 0 (0%) 7-10: 6 (16%) >10: 4 (11%)	0.002	NR	~3.75± NR	NR	~2.48± NR	NR
	Placebo (5 weeks)	44	0: 0 (0%) <1: 5 (11%) 1: 11 (25%) 2-3: 17 (39%) 4-6: 3 (7%) 7-10: 4 (9%) >10: 4 (9%)	0: 5 (11%) <1: 6 (14%) 1: 14 (32%) 2-3: 12 (27%) 4-6: 1 (2%) 7-10: 3 (7%) >10: 3 (7%)	not signi-ficant (p NR)		~3.03± NR		~2.42± NR	

Abbreviations
~ = approximate estimation extracted from figure, NR = not reported, SD = standard deviation.
Notes
a = A 6-point scale of frequency of vertigo attacks per week: 0 = 0, 1 = <1, 2 = 1, 3 = 2-3, 4 = 4-6, 5 = 7-10, 6 = >10.

Table 32. Efficacy results on betahistine for vertigo – vertigo attack duration

Reference	Intervention (dose; duration)	Sample size analysed	Vertigo attack duration			
	Comparator (duration)		Pre-treatment n (%) patients	Post-treatment n (%) patients	p-value within group	p-value between group
Oosterveld et al 1989	Betahistine (48 mg/day; 5 weeks)	38	0 min: 0 (0%) <5 min: 14 (37%) 5-60 min: 15 (39%) 1-6 hours: 5 (13%) >6 hours: 4 (11%)	0 min: 4 (11%) <5 min: 14 (37%) 5-60 min: 11 (29%) 1-6 hours: 6 (16%) >6 hours: 3 (8%)	not signi-ficant (p NR)	NR
	Placebo (5 weeks)	44	0 min: 0 (0%) <5 min: 13 (30%) 5-60 min: 8 (18%) 1-6 hours: 13 (30%) >6 hours: 10 (23%)	0 min: 5 (11%) <5 min: 11 (25%) 5-60 min: 12 (27%) 1-6 hours: 11 (25%) >6 hours: 5 (11%)	0.03	

Abbreviations
min = minutes, NR = not reported.

Table 33. Efficacy results on betahistine for vertigo – vertigo attack severity

Reference	Intervention (dose; duration)	Sample size analysed	Vertigo attack severity				Vertigo attack severity score			
	Comparator (duration)		Pre-treatment n (%) patients	Post-treatment n (%) patients	p-value within group	p-value between group	Pre-treatment mean± SD score	p-value between group	Post-treatment mean± SD score	p-value between group
Conraux et al 1988	Betahistine (close to 48 mg/day; 3 months)	27	-	-	-	-	5-point scale: ~2.15± NR[a]	NR	5-point scale: ~1.13± NR[a]	significant (p NR)
	Placebo (3 months)	20	-	-	-		5-point scale: ~2.15± NR[a]		5-point scale: ~1.58± NR[a]	
Oosterveld et al 1989	Betahistine (48 mg/day; 5 weeks)	38	0: 10 (26%) 1: 16 (42%) 2: 8 (21%) 3: 4 (11%)	0: 20 (53%) 1: 14 (37%) 2: 4 (11%) 3: 0 (0%)	0.002	NR	4-point scale: ~1.17± NR[b]	NR	4-point scale: ~0.57± NR[b]	NR
	Placebo (5 weeks)	44	0: 9 (21%) 1: 19 (43%) 2: 7 (16%) 3: 9 (21%)	0: 16 (36%) 1: 11 (25%) 2: 12 (27%) 3: 5 (11%)	not significant (p NR)		4-point scale: ~1.37± NR[b]		4-point scale: ~1.16± NR[b]	

Abbreviations
~ = approximate estimation extracted from figure, NR = not reported, SD = standard deviation.
Notes
a = A 5-point scale of severity of vertigo, ranging from 1 (simple discomfort not hindering activity) to 5 (bed rest).
b = A 4-point scale of severity of vertigo attacks: 0 = no influence, 1 = at times unable to work, 2 = staying home, 3 = staying in bed.

Canty et al 1981 reported an improvement of vertigo symptoms after 8 weeks of treatment with betahistine in 7 (54%) patients and with placebo in 8 (62%) patients (***Table 34***).[33] The calculated risk ratio was not statistically significant (RR 0.88 [95% CI 0.45 to 1.69]; very low certainty evidence; ***Table 46***).

Table 34. Efficacy results on betahistine for vertigo – investigator-reported vertigo change

Reference	Intervention (dose; duration)	Sample size analysed	Severity of vertigo symptoms		Investigator's evaluation of vertigo post-treatment versus pre-treatment				
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Unchanged[a] n (%) patients	Improved[a] n (%) patients	Worsened[a] n (%) patients	p-value between group	Calculated RR (95% CI) vertigo improved
Canty et al 1981	Betahistine (32 mg/day; 8 weeks)	13	NR	0.71	5 (38%)	7 (54%)	1 (8%)	0.62	0.88 (0.45 to 1.69)
	Placebo (8 weeks)	13	NR		5 (38%)	8 (62%)	0 (0%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SD = standard deviation.
Notes
a = Not defined.

6.2.5.2.2 Outcome health-related quality of life

For patients with vertigo treated with betahistine no data was reported on the secondary outcome HRQoL.

6.2.5.3 Cinnarizine for tinnitus

For patients with tinnitus treated with cinnarizine the primary efficacy outcome of interest was tinnitus. Results reported on the objective evaluation of tinnitus in the RCT of Podoshin et al 1991 with relevant data missing for valid data interpretation (i.e. missing pre-treatment data) was extracted and enclosed in ***Appendix D.***; this data was not included in the data synthesis.[36]

6.2.5.3.1 Outcome tinnitus

After 10 weeks of treatment Podoshin et al 1991 reported very small changes in tinnitus scores, with an improvement of 4.8% (from score 2.1 to 2.0) of the mean tinnitus disturbance during activity in the cinnarizine group and 0% (score 2.3) in the placebo group, and respectively 6.9% (from score 2.9 to 2.7) and 1.7% (from score 2.9 to 2.85) during rest (***Table 35***).[36] These treatment differences in tinnitus disturbance were not statistically significant (very low certainty evidence; ***Table 47***).

Table 35. Efficacy results on cinnarizine for tinnitus – tinnitus disturbance

Reference	Intervention (dose; duration)	Sample size anlysed	Weekly score of disturbance degree of tinnitus during activity[a]					
	Comparator (duration)		Pre-treatment mean±SD	Post-treatment mean±SD	Improvement in mean score (%)	p-value between group	Calculated mean absolute change ±SD	Calculated treatment difference (95% CI)
Podoshin et al 1991	Cinnarizine (75 mg/day; 10 weeks)	10	2.1±NR	2.0±NR	4.8%	not significant (p NR)	-0.1±NR	-0.1 (NR)
	Placebo (10 weeks)	20	2.3±NR	2.3±NR	0%		0±NR	

Abbreviations
CI = confidence interval, NR = not reported, SD = standard deviation.
Notes
a = Subjective severity rating for tinnitus disturbance during activity: 0=no tinnitus, 1=mild tinnitus without disturbance, 2=moderate, which disturbs but does not affect activity, 3=severe, which affects activity, 4=very severe, which renders activity impossible. Moderate degrees of disturbance were rated 0-2 and severe degrees of disturbance were rated 3-4.

Table 35 continued. Efficacy results on cinnarizine for tinnitus – tinnitus disturbance

Reference	Intervention (dose; duration)	Sample size analysed	Weekly score of disturbance degree of tinnitus during rest[b]					
	Comparator (duration)		Pre-treatment mean±SD	Post-treatment mean±SD	Improvement in mean score (%)	p-value between group	Calculated mean absolute change ±SD	Calculated treatment difference (95% CI)
Podoshin et al 1991	Cinnarizine (75 mg/day; 10 weeks)	10	2.9±NR	2.7±NR	6.9%	not significant (p NR)	-0.2±NR	-0.15 (NR)
	Placebo (10 weeks)	20	2.9±NR	2.85±NR	1.7%		-0.05±NR	

Abbreviations
CI = confidence interval, NR = not reported, SD = standard deviation.
Notes
b = Subjective severity rating for tinnitus disturbance during rest: 0=no tinnitus, 1=mild tinnitus without disturbance, 2=moderate, which disturbs but does not affect sleep, 3=severe, which affects sleep, 4=very severe, which causes severe insomnia and causes spontaneous arousals. Moderate degrees of disturbance were rated 0-2 and severe degrees of disturbance were rated 3-4.

In the cinnarizine arm 1 (10%) patient and in the placebo arm 1 (5%) patient reported an improvement of tinnitus symptoms after 10 weeks of treatment (***Table 36***). The calculated risk ratio was not statistically significant (RR 2.00 [95% CI 0.14 to 28.76]; very low certainty evidence; ***Table 47***). The patient who reacted to the cinnarizine treatment had severe tinnitus.

Table 36. Efficacy results on cinnarizine for tinnitus – patient-reported tinnitus change

Reference	Intervention (dose; duration)	Sample size analysed	Patient-reported tinnitus change			
	Comparator (duration)		Unchanged[a] n (%) patients	Improved[a] n (%) patients	p-value between group	Calculated RR (95% CI) tinnitus improved
Podoshin et al 1991	Cinnarizine (75 mg/day; 10 weeks)	10	9 (90%)	1 (10%)	NR	2.00 (0.14 to 28.76)
	Placebo (10 weeks)	20	19 (95%)	1 (5%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio.
Notes
a = Not defined.

6.2.5.3.2 Outcome health-related quality of life

For patients with tinnitus treated with cinnarizine no data was reported on the secondary outcome HRQoL.

6.2.5.4 Cinnarizine with dimenhydrinate for vertigo

For patients with vertigo treated with cinnarizine with dimenhydrinate the primary efficacy outcome of interest was vertigo.

6.2.5.4.1 Outcome vertigo

Both included RCTs on patients with vertigo reported statistically significant treatment differences in their primary efficacy outcome mean vertigo score in favour of cinnarizine with dimenhydrinate compared with placebo (moderate certainty evidence; ***Table 50***).[37,38]

On a scale ranging from 0 (no symptoms) to 3 (strong symptoms), Otto et al 2008 reported a statistically significant difference between the mean changes in vertigo score in patients treated with cinnarizine with dimenhydrinate (-0.98±0.42) and placebo (+0.07±0.22; ***Table 37***).[37] The mean vertigo baseline score in the cinnarizine with dimenhydrinate arm (1.4) was higher than in the placebo arm (1.02) at a 20% significance level, therefore also adjusted mean changes calculated by analysis of covariance were reported. The difference in adjusted mean changes of -1.15 (standard deviation not reported) for cinnarizine with dimenhydrinate treatment and +0.15 (standard deviation not reported) for placebo was also statistically significant.

Pytel et al 2007 reported a statistically significant difference between the mean changes in vertigo score on a scale ranging from 0 (no symptoms) to 4 (very severe symptoms) in patients treated with cinnarizine with dimenhydrinate (-1.37±0.66) and placebo (-0.76±0.48), with an adjusted difference in least squares (analysis of covariance) mean vertigo score of -0.56 (95% CI -0.38 to -0.75; ***Table 37***).[38] Furthermore, the clinical relevance of the treatment effect of cinnarizine with dimenhydrinate was supported by statistically significant differences from the Mann-Whitney estimator (***Table 37***) and the number of patients in the study arms with a mean vertigo score of 0 (i.e. symptom free) and <0.5 (i.e. no or minor vertigo symptoms) after 4 weeks of treatment (***Table 37 continued***).

Table 37. Efficacy results on cinnarizine with dimenhydrinate for vertigo – mean vertigo score

Reference	Intervention (dose; duration)	Sample size analysed	Vertigo attack intensity, mean vertigo score												
	Comparator (duration)		Pre-treatment (mean± SD)	p-value between group	Post-treatment (mean± SD)	p-value between group	Mean change± SD	p-value within group	p-value between group	Post-treatment adjusted LS mean (95%)[a]	p-value between group	Difference in adjusted LS mean (95% CI)	Cohen's standardised difference (95% CI)	Mann-Whitney estimator (95% CI)	Calculated treatment difference (95% CI)
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	11	4-point scale: ~1.4±NR[b]	0.093[c]	4-point scale: ~0.4±NR[b]	<0.001	4-point scale: -0.98±0.42 (adjusted mean[d] -1.15±NR)[b]	<0.01	<0.001 (adjusted mean p<0.001)	-	-	-	-	-	-1.3 (NR)
	Placebo (4 weeks)	11	4-point scale: ~1.02±NR[b]		4-point scale: ~1.08±NR[b]		4-point scale: +0.07±0.22 (adjusted mean[d] +0.15±NR)[b]	not significant (p NR)		-		-	-	-	
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	61	5-point scale: 1.85±0.54[e]	not significant (p NR)	5-point scale: 0.45±0.51[e]	NR	5-point scale: -1.37±0.66[e]	NR	<0.001	5-point scale: 0.43 (0.30 to 0.56)[e]	<0.001	5-point scale: -0.56 (-0.38 to -0.75)[e]	5-point scale: -1.06 (-0.67 to -1.45)[e f]	5-point scale: 0.77 (0.68 to 0.84)[e g]	Not applicable, see adjusted LS mean
	Placebo (4 weeks)	58	5-point scale: 1.74±0.63[e]		5-point scale: 1.01±0.69[e]		5-point scale: -0.76±0.48[e]	NR		5-point scale: 0.99 (0.86 to 1.13)[e]					

Abbreviations

~ = approximate estimation extracted from figure, CI = confidence interval, LS = least squares (analysis of covariance), NR = not reported, SD = standard deviation.

Notes

a = In the case of insufficient homogeneity of the initial distributions, confirmatory analysis was performed by analysis of covariance (ANCOVA) with adjustment of the means at the end of treatment using the initial values as covariates.

b = Mean vertigo score defined as the mean of the intensities of 6 vertigo symptoms and vertigo as a consequence of 6 trigger factors: unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, swaying, and vertigo due to change of position, bowing, getting up, walking, head movements, and eye movements; 4-point scale ranging from 0=no symptoms to 3=strong symptoms.

c = Imbalance in initial distribution at the 20% significance level.

d = Adjusted mean calculated after adjustment for non-homogeneous initial distribution by analysis of covariance.

e = Mean vertigo score defined as the mean intensity of 12 vertigo symptoms: dysstasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, blackout, and vertigo after change of position, bowing, getting up, traveling by car or train, head movement, and eye movement; 5-point scale ranging from 0=no symptoms to 4=very severe symptoms.

f = The effect size for cinnarizine with dimenhydrinate versus placebo was >0.71, indicating a large effect; the lower limit of the 95% CI was above 0.64, indicating a medium effect size.

g = Indicating a clinically relevant difference.

Table 37 continued. Efficacy results on cinnarizine with dimenhydrinate for vertigo – mean vertigo score

Reference	Intervention (dose; duration)	Sample size analysed	No vertigo symptoms (mean vertigo score=0)				No or minor vertigo symptoms (mean vertigo score ≤0.5)				50% change in mean vertigo score			
	Comparator (duration)		Post-treatment n (%) patients	Post-treatment 95% CI	p-value between group	Post-treatment OR (95% CI)	Post-treatment n (%) patients	Post-treatment 95% CI	p-value between group	Post-treatment OR (95% CI)	Post-treatment n (%) patients	Post-treatment 95% CI	p-value between group	Post-treatment OR (95% CI)
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	11	-	-	-	-	-	-	-	-	-	-	-	-
	Placebo (4 weeks)	11	-	-			-	-			-	-		
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	61	13 (21.3%)	0.12 to 0.34	0.005	7.58 (1.57 to 71.50)	38 (62.3%)	0.49 to 0.74	<0.001	5.19 (2.20 to 12.47)	51 (83.6%)	0.72 to 0.92	<0.001	5.86 (2.33 to 15.30)
	Placebo (4 weeks)	58	2 (3.4%)	0.004 to 0.12			14 (24.1%)	0.14 to 0.37			27 (46.6%)	0.33 to 0.60		

Abbreviations
CI = confidence interval, OR = odds ratio.

As secondary efficacy outcome the RCTs reported the overall efficacy of cinnarizine with dimenhydrinate rated by the patients and investigator on a 5-point verbal rating scale: very much improved, much improved, slightly improved, not improved, or deteriorated. In the cinnarizine with dimenhydrinate arm 8 (73%) patients and in the placebo arm 0 (0%) patients rated much or very much improvement in vertigo symptoms after 4 weeks of treatment in the RCT of Otto et al 2008, and respectively 47 (80%) and 29 (51%) patients in the RCT of Pytel et al 2007 (***Table 38***).[37,38] The investigators' rating of overall efficacy of treatment was similar. The pooled risk ratio was not statistically significant (RR 3.44 [95% CI 0.38 to 31.02]; Tau^2=1.858, Q-value=2.884, df=1, p=0.089, I^2=65.323, prediction interval not estimated; very low certainty evidence; ***Table 50***). A judgement of the unexplained statistical heterogeneity based on 2 studies is not reliable.

Table 38. Efficacy results on cinnarizine with dimenhydrinate for vertigo – patient and investigator – reported overall efficacy treatment

Reference	Intervention (dose; duration)	Sample size analysed	Patients' and investigators' rating overall efficacy treatment[a] (vertigo much or very much improved)			
	Comparator (duration)		Post-treatment n (%) patients	p-value between group	Calculated RR (95% CI) vertigo improved	Pooled RR (95% CI) vertigo improved
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mgdimenhydrinate; 4 weeks)	11	8 (73%)	<0.001	17.00 (1.10 to 262.66)	3.44 (0.38 to 31.02)
	Placebo (4 weeks)	11	0 (0%)			
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	59	47 (80%)	NR	1.57 (1.18 to 2.08)	
	Placebo (4 weeks)	57	29 (51%)			

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio.
Notes
a = Patients and investigators rated the overall efficacy of study treatment using a 5-point verbal rating scale: very much improved, much improved, slightly improved, not improved and deteriorated.

6.2.5.4.2 Outcome health-related quality of life

For patients with vertigo treated with cinnarizine with dimenhydrinate no data was reported on the secondary outcome HRQoL.

6.2.6 Findings effectiveness

6.2.6.1 Betahistine

Following the planned approach in the HTA protocol (i.e. to proceed with the subsequent search step for comparative non-randomised studies in case overall less than 2 RCTs were found for the primary efficacy and safety outcomes) no systematic literature search for comparative non-randomised studies was performed, as 4 RCTs were found with the systematic literature search for betahistine in patients with Ménière's disease and 3 RCTs for betahistine in patients with vertigo.

6.2.6.2 Cinnarizine

Though for cinnarizine in patients with tinnitus one RCT was found, it was decided to deviate from the HTA protocol and not proceed with the subsequent search step for comparative non-randomised studies. Since data reporting in the included RCTs (i.e. the study design with the highest level of evidence) was limited, it was not expected that a search for comparative non-randomised studies would result in additional relevant evidence.

6.2.6.3 Cinnarizine with dimenhydrinate

Following the planned approach in the HTA protocol no systematic literature search for comparative non-randomised studies was performed, as 2 RCTs were found with the systematic literature search for cinnarizine with dimenhydrinate in patients with vertigo.

6.2.7 Findings safety

The findings on the safety outcomes are reported in separate sections for the 4 groups betahistine for Ménière's disease (***Section 6.2.6.1***), betahistine for vertigo (***Section 6.2.6.2***), cinnarizine for tinnitus (***Section 6.2.6.3***), and cinnarizine with dimenhydrinate for vertigo (***Section 6.2.6.4***).

6.2.7.1 Betahistine for Ménière's disease

Within the 9-month treatment period in the RCT of Adrion et al 2016 one or more serious adverse events occurred in 12 (17%) patients with Ménière's disease in the low-dose betahistine arm and in 11 (15%) patients in the placebo arm (***Table 39***).[39] In the RCT of Mira et al 2003 no serious adverse events were reported in the betahistine or placebo arm during 3 months of treatment.[41] The pooled risk ratio for the occurrence of serious adverse events up to 9 months was not statistically significant (RR 1.12 [95% CI 0.53 to 2.38]; low certainty evidence; ***Table 45***). Only the RCT of Adrion et al 2016 provided data for this risk ratio.

Table 39. Safety results on betahistine for Ménière's disease – serious adverse events

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	≥1 SAE n (%) patients	p-value between group	Calculated RR (95% CI)	Pooled RR (95% CI)
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	72	12 (17%)	NR	1.12 (0.53 to 2.38)	1.12 (0.53 to 2.38)
	Betahistine high dose (144 mg/day; 9 months)	*74*	*14 (19%)*			
	Placebo (9 months)	74	11 (15%)			

Mira et al 2003	Betahistine (32 mg/day; 3 months)	41	0 (%)	NR	not estimable
	Placebo (3 months)	40	0 (%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SAE = serious adverse event.
Notes
*Data on off-label betahistine use will be described in **Section 9.4**.*

Mira et al 2003 reported a low occurrence ranging from 0% to 3% of the other adverse events of interest gastro-intestinal disturbance, drowsiness and dry mouth; headache was reported by 5 (12%) patients treated with betahistine versus 0 (0%) patients treated with placebo (***Table 40***).[41] The calculated risk ratios for these other adverse events were not statistically significant with wide confidence intervals: headache (RR 10.74 [95% CI 0.61 to 188.05]), gastralgia (RR 0.33 [95% CI 0.014 to 7.76]), abdominal pain (RR 0.33 [95% CI 0.014 to 7.76]), drowsiness (RR 2.93 [95% CI 0.12 to 69.83]), and dry mouth (not estimable).

Table 40. Safety results on betahistine for Ménière's disease – other adverse events

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Headache n (%) patients	p-value between group	Calculated RR (95% CI)	Gastro-intestinal disturbance n (%) patients	p-value between group	Calculated RR (95% CI)
Mira et al 2003	Betahistine (32 mg/day; 3 months)	41	5 (12%)	NR	10.74 (0.61 to 188.05)	gastralgia: 0 (0%) abdominal pain: 0 (0%)	NR	gastralgia: 0.33 (0.014 to 7.76)
	Placebo (3 months)	40	0 (0%)			gastralgia: 1 (3%) abdominal pain: 1 (3%)		abdominal pain: 0.33 (0.014 to 7.76)

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SAE = serious adverse event.

Table 40 continued. Safety results on betahistine for Ménière's disease – other adverse events

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Sleep disturbance n (%) patients	p-value between group	Calculated RR (95% CI)	Dry mouth n (%) patients	p-value between group	Calculated RR (95% CI)
Mira et al 2003	Betahistine (32 mg/day; 3 months)	41	drowsiness: 1 (2%)	NR	2.93 (0.12 to 69.83)	0 (0%)	NR	not estimable
	Placebo (3 months)	40	drowsiness: 0 (0%)			0 (0%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SAE = serious adverse event.

6.2.7.2 Betahistine for vertigo

No serious adverse events were reported in the betahistine or placebo arm in the 3 included RCTs on betahistine treatment for up to 3 months in patients with vertigo (***Table 41***; RR not estimable; very low certainty evidence; ***Table 46***).[33–35]

Table 41. Safety results on betahistine for vertigo – serious adverse events

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	≥1 SAE n (%) patients	p-value between group	Calculated RR (95% CI)	Pooled RR (95% CI)
Canty et al 1981	Betahistine (32 mg/day; 8 weeks)	13	0 (0%)	NR	not estimable	not estimable
	Placebo (8 weeks)	13	0 (0%)			
Conraux et al 1988	Betahistine (close to 48 mg/day; 3 months)	NR[a], 27 at 3 months	0 (0%)	NR	not estimable	
	Placebo (3 months)	NR[a], 20 at 3 months	0 (0%)			
Oosterveld et al 1989	Betahistine (48 mg/day; 5 weeks)	38	0 (0%)	NR	not estimable	
	Placebo (5 weeks)	44	0 (0%)			

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SAE = serious adverse event.
Notes
a = Sample size at baseline was not reported.

The other adverse event of interest gastrointestinal disturbance was reported as gastralgia by Conraux et al 1988 in 4 (15%) patients treated with betahistine and in 2 (10%) patients treated with placebo (***Table 42***), with a statistically non-significant calculated risk ratio of 1.48 (95% CI 0.30 to 7.31).[34]

Table 42. Safety results on betahistine for vertigo – other adverse events

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Gastrointestinal disturbance n (%) patients	p-value between group	Calculated RR (95% CI)
Conraux et al 1988	Betahistine (close to 48 mg/day; 3 months)	NR, 27 at 3 months	gastralgia: 4 (15%)	NR	1.48 (0.30 to 7.31)
	Placebo (3 months)	NR, 20 at 3 months	gastralgia: 2 (10%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio.

6.2.7.3 Cinnarizine for tinnitus

For patients with tinnitus treated with cinnarizine no data was reported on the primary outcome serious adverse events or secondary outcome other adverse events.

6.2.7.4 Cinnarizine with dimenhydrinate for vertigo

No serious adverse events were encountered in the 2 included RCTs on cinnarizine with dimenhydrinate treatment for 4 weeks compared with placebo in patients with vertigo (***Table 43***; RR not estimable; low certainty evidence; ***Table 50***).[37,38]

Table 43. Safety results on cinnarizine with dimenhydrinate for vertigo – serious adverse events

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	≥1 SAE n (%) patients	p-value between group	Calculated RR (95% CI)	Pooled RR (95% CI)
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	11	0 (0%)	NR	not estimable	not estimable
	Placebo (4 weeks)	13	0 (0%)			
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	61	0 (0%)	NR	not estimable	
	Placebo (4 weeks)	60	0 (0%)			

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio, SAE = serious adverse event.

The other adverse event of interest gastrointestinal disturbance was reported as upset gastrointestinal tract by Otto et al 2008 in 1 (9%) patient treated with cinnarizine with dimenhydrinate and in 0 (0%) patients treated with placebo (***Table 44***), with a statistically non-significant RR of 3.50 (95% CI 0.16 to 78.19).[37] Somnolence was reported by Pytel et al 2007 in 5 (8%) patients treated with cinnarizine with dimenhydrinate and in 2 (3%) patients treated with placebo (RR 2.46 [95% CI 0.49 to 12.19]) and headache did not occur as adverse event in the study arms (RR not estimable).[38]

Table 44. Safety results on cinnarizine with dimenhydrinate for vertigo – other adverse events

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Headache n (%) patients	p-value between group	Calculated RR (95% CI)
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	11	-	-	not estimable
	Placebo (4 weeks)	13	-		
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	61	0 (0%)	NR	
	Placebo (4 weeks)	60	0 (0%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio.

Table 44 continued. Safety results on cinnarizine with dimenhydrinate for vertigo – other adverse events

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Gastrointestinal disturbance n (%) patients	p-value between group	Calculated RR (95% CI)	Sleep disturbance n (%) patients	p-value between group	Calculated RR (95% CI)
Otto et al 2008	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	11	upset gastrointestinal tract: 1 (9%)	NR	3.50 (0.16 to 78.19)	-	-	2.46 (0.49 to 12.19)
	Placebo (4 weeks)	13	upset gastrointestinal tract: 0 (0%)			-		
Pytel et al 2007	Cinnarizine with dimenhydrinate (60 mg cinnarizine and 120 mg dimenhydrinate; 4 weeks)	61	-	-		somnolence: 5 (8%)	NR	
	Placebo (4 weeks)	60	-			somnolence: 2 (3%)		

Abbreviations
CI = confidence interval, NR = not reported, RR = risk ratio.

6.2.8 GRADE Summary of Findings Table

6.2.8.1 Betahistine for Ménière's disease

Table 45. GRADE summary of findings table – betahistine for Ménière's disease

Population: Patients with Ménière's disease
Intervention: Betahistine, licensed use (24-48 mg/day)
Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Efficacy						
Vertigo – vertigo attack frequency follow-up: 9 months	Monthly decay rate 0.76 (0.71 to 0.82)	NR	adjusted rate ratio 1.04 (0.94 to 1.14)	135[a] (1 RCT[39])	⊕⊕⊕◯ Moderate[b]	-
Tinnitus – tinnitus intensity follow-up: 9 months	Mean absolute change -0.56 (-6.02 to 4.91)	Mean absolute change +7.07 (0.53 to 13.60)	aMD[c] +1.40 (-5.10 to 7.90)	59 (1 RCT[39])	⊕⊕◯◯ Low[d]	Assessed with PTA in decibel; a decrease in decibel corresponds to less tinnitus, although the observed changes are very small
Hearing loss – PTA follow-up: 9 months	Mean absolute change	Mean absolute change	aMD[c]	74 to 96[e] (1 RCT[39])	⊕⊕◯◯ Low[f]	Assessed with PTA in decibel; a decrease in decibel corresponds to less hearing loss, although the observed changes are very small
	250 Hz: -5.53 (-9.01 to -2.06)	-1.99 (-5.20 to 1.22)	+0.33 (-3.13 to 3.79)			
	500 Hz: -4.37 (-8.39 to -0.36)	+0.29 (-3.64 to 4.21)	+1.99 (-2.64 to 6.62)			
	1000 Hz: -5.44 (-9.21 to -1.68)	-0.60 (-4.29 to 3.09)	+2.83 (-1.93 to 7.59)			
	2000 Hz: -1.53 (-4.94 to 1.87)	+0.61 (-2.58 to 3.80)	+1.67 (-2.41 to 5.74)			
Disease-specific HRQoL – DHI follow-up: 9 months comparison: placebo	Mean absolute change -0.50 (-0.69 to -0.31)	Mean absolute change -0.36 (-0.55 to -0.17)	aMD[c] +0.08 (-0.17 to 0.33)	113 (1 RCT[39])	⊕⊕⊕◯ Moderate[g]	Mean total score range per answer 0 (best) to 4 (worst)
Disease-specific HRQoL – DHI follow-up: 1 month comparison: no treatment	Mean absolute change -0.8 (NR)	Mean absolute change -6.9 (NR)	MD -6.1 (NR; significant post-treatment)	41 (1 RCT[41])	⊕◯◯◯ Very low[h i]	Score range total 0 (best) to 100 (worst)
Disease-specific HRQoL – VDADL follow-up: 9 months	Mean absolute change -0.20 (-0.41 to 0.00)	Mean absolute change -0.26 (-0.46 to -0.06)	aMD[c] -0.05 (-0.32 to 0.22)	115 (1 RCT[39])	⊕⊕⊕◯ Moderate[g]	Score range total 1 (best) to 10 (worst)
Disease-specific HRQoL– MiniTF12 follow-up: 9 months	Mean absolute change -0.12 (-0.22 to -0.02)	Mean absolute change -0.11 (-0.21 to -0.01)	aMD[c] -0.007 (-0.14 to 0.13)	112 (1 RCT[39])	⊕⊕⊕◯ Moderate[g]	Score range total 0 (best) to 24 (worst)

HRQoL	NR					
Effectiveness						
NA						
Safety						
≥1 serious adverse event follow-up: up to 9 months	11/74	12/72	RR 1.12 (0.53 to 2.38)	227 (2 RCTs[39,41])	⨁⨁◯◯ Low[i k]	RR based on 1 RCT; 0 cases in the betahistine and placebo arm of the other RCT

Abbreviations
aMD = adjusted mean difference, CI = confidence interval, DHI = dizziness handicap inventory, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, MD = mean difference, MiniTF12 = mini-tinnitus impairment questionnaire score based on 12 items, NA = not applicable, NR = not reported, PTA = pure tone audiometry, RCT = randomised controlled trial, RR = risk ratio, VDADL = vestibular disorders activities of daily living.
Notes
a = Sample size analysed not reported, pseudobaseline data for this outcome was reported for 135 participants.
b = Certainty of evidence downgraded due to serious risk of bias (see ***Section 6.2.3.1.1***).
c = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created).
d = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.1.2***).
e = Sample size differed for the 4 PTA frequencies.
f = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.1.3***).
g = Certainty of evidence downgraded due to serious risk of bias (see ***Section 6.2.3.1.4***).
h = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.1.4***).
i = Certainty of evidence downgraded due to serious imprecision (no estimate for precision reported).
j = Certainty of evidence downgraded due to serious risk of bias (see ***Section 6.2.3.1.5***).
k = Certainty of evidence downgraded due to serious imprecision (wide 95% CI including the null effect).

6.2.8.2 Betahistine for vertigo

Table 46. GRADE summary of findings table – betahistine for vertigo

Population: Patients with diverse vertigo aetiologies
Intervention: Betahistine, licensed use (24-48 mg/day)
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Efficacy						
Vertigo – vertigo attack frequency follow-up: 5 weeks	Compared to baseline, a statistically significant decrease in the betahistine arm and non-significant decrease in the placebo arm			82 (1 RCT[35])	⊕◯◯◯ Very low[a b]	-
Vertigo – vertigo attack duration follow-up: 5 weeks	Compared to baseline, a non-significant decrease in the betahistine arm and statistically significant decrease in the placebo arm			82 (1 RCT[35])	⊕◯◯◯ Very low[a b]	-
Vertigo – vertigo attack severity follow-up: up to 3 months	Compared to baseline, a statistically significant decrease in the betahistine arm and non-significant decrease in the placebo arm in 1 RCT and a statistically significant difference in decrease of vertigo attack severity in favour of betahistine in 1 RCT			129 (2 RCTs[34,35])	⊕◯◯◯ Very low[a b]	-
Vertigo – investigator-reported vertigo improvement follow-up: 8 weeks	8/13	7/13	RR 0.88 (0.45 to 1.69)	26 (1 RCT[33])	⊕◯◯◯ Very low[a c]	-
Tinnitus	NA					
Hearing loss	NA					
Disease-specific HRQoL	NR					
HRQoL	NR					
Effectiveness						
NA						
Safety						
≥1 serious adverse event follow-up: up to 3 months	0/77	0/78	Not estimable	155 (3 RCTs[33–35])	⊕◯◯◯ Very low[d e]	0 cases in the betahistine and placebo arm of 3 RCTs

Abbreviations
CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, NA = not applicable, NR = not reported, RCT = randomised controlled trial, RR = risk ratio.
Notes
a = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.2.1***).
b = Certainty of evidence downgraded due to serious imprecision (no estimate for precision reported).
c = Certainty of evidence downgraded due to serious imprecision (wide 95% CI including the null effect).
d = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.2.3***).
e = Certainty of evidence downgraded due to serious imprecision (no estimate for precision reported).

6.2.8.3 Cinnarizine for tinnitus

Table 47. GRADE summary of findings table – cinnarizine for tinnitus

Population: Patients with idiopathic subjective tinnitus
Intervention: Cinnarizine, licensed use (75 mg/day)
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Cinnarizine				
Efficacy						
Vertigo	NA					
Tinnitus – tinnitus disturbance during activity follow-up: 10 weeks	Change in mean score 0 (NR)	Change in mean score -0.1 (NR)	MD mean score -0.1 (NR; not significant)	30 (1 RCT[36])	⊕◯◯◯ Very low[a b]	Score range 0 (best) to 4 (worst)
Tinnitus – tinnitus disturbance during rest follow-up: 10 weeks	Change in mean score -0.05 (NR)	Change in mean score -0.2 (NR)	MD mean score -0.15 (NR; not significant)	30 (1 RCT[36])	⊕◯◯◯ Very low[a b]	Score range 0 (best) to 4 (worst)
Tinnitus – patient-reported tinnitus improvement follow-up: 10 weeks	1/20	1/10	RR 2.00 (0.14 to 28.76)	30 (1 RCT[36])	⊕◯◯◯ Very low[a c]	-
Hearing loss	NA					
Disease-specific HRQoL	NR					
HRQoL	NR					
Effectiveness						
NA						
Safety						
≥1 serious adverse event	NR					

Abbreviations
CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, MD = mean difference, NA = not applicable, NR = not reported, RCT = randomised controlled trial, RR = risk ratio.
Notes
a = Certainty of evidence downgraded due to very serious risk of bias (see ***Section 6.2.3.3.1***).
b = Certainty of evidence downgraded due to serious imprecision (no estimate for precision reported).
c = Certainty of evidence downgraded due to very serious imprecision (very wide 95% confidence interval including the null effect).

6.2.8.4 Cinnarizine with dimenhydrinate for vertigo

Table 48. GRADE summary of findings table – cinnarizine with dimenhydrinate for vertigo

Population: Patients with diverse vertigo aetiologies
Intervention: Cinnarizine (60 mg/day) with dimenhydrinate (120 mg/day), licensed use
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Cinnarizine with dimenhydrinate				
Efficacy						
Vertigo – mean vertigo score follow-up: 4 weeks	A statistically significant aMD[a] of -1.3 (NR) on a 4-point scale in favour of cinnarizine with dimenhydrinate in 1 RCT and a statistically significant aMD[a] of -0.56 (-0.38 to -0.75) on a 5-point scale in favour of cinnarizine with dimenhydrinate in 1 RCT			141 (2 RCTs[37,38])	⊕⊕⊕◯ Moderate[b]	4-point scale range 0 (best) to 3 (worst); 5-point scale range 0 (best) to 4 (worst)
Vertigo – patient and investigator-reported vertigo improvement follow-up: 4 weeks	29/68	55/70	RR 3.44 (0.38 to 31.02)	138 (2 RCTs[37,38])	⊕◯◯◯ Very low[b c]	-
Tinnitus	NA					
Hearing loss	NA					
Disease-specific HRQoL	NR					
HRQoL	NR					
Effectiveness						
NA						
Safety						
≥1 serious adverse event follow-up: 4 weeks	0/73	0/72	Not estimable	145 (2 RCTs[37,38])	⊕⊕◯◯ Low[d e]	0 cases in the cinnarizine with dimenhydrinate and placebo arm of 2 RCTs

Abbreviations
aMD = adjusted mean difference, CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, NA = not applicable, NR = not reported, RCT = randomised controlled trial, RR = risk ratio, SD = standard deviation.
Notes
a = Adjusted mean calculated after adjustment for non-homogeneous initial distribution by analysis of covariance.
b = Certainty of evidence downgraded due to serious risk of bias (see ***Section 6.2.3.4.1***).
c = Certainty of evidence downgraded due to very serious imprecision (very wide 95% confidence interval including the null effect).
d = Certainty of evidence downgraded due to serious risk of bias (see ***Section 6.2.3.4.3***).
e = Certainty of evidence downgraded due to serious imprecision (no estimate for precision reported).

7. Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

No studies were identified during the systematic literature search on cost-effectiveness.

Cost-effectiveness analyses were only performed for populations for which the clinical systematic literature search has shown that there is evidence for an effect of treatment. Only for cinnarizine with dimenhydrinate in patients with vertigo caused by other disorders than Ménière's disease evidence was found of a positive treatment effect compared to placebo. Therefore, a cost-effectiveness model was only developed for this population. Since there was no information on utility values for this population, the incremental cost-effectiveness ratio was expressed in cost per mean vertigo score (MVS) point reduced, with MVS expressed on a 5-point scale. The results of the cost-effectiveness analyses conducted for Switzerland showed that treatment with cinnarizine with dimenhydrinate resulted in lower costs and additional benefit, compared to no treatment. As such, treatment with cinnarizine with dimenhydrinate dominated no treatment for the treatment of vertigo caused by other disorders than Ménière's disease. Scenario analyses showed the robustness of the results. Only if costs related to non-response were ignored, the incremental cost-effectiveness ratio was positive, but remained under CHF 100 per MVS point reduced. Approximately 91% of 1,000 probabilistic sensitivity analysis iterations showed cost savings; 70% of 1,000 iterations resulted in cost savings and health benefits.

Despite the lack of evidence for a positive treatment effect of betahistine and cinnarizine, these treatments are currently reimbursed in Switzerland, and hence associated with a budgetary impact. Budget impact analyses estimated that total costs of betahistine for treatment of Ménière's disease or vertigo were CHF 17.2 million over a 5-year period. Expenditures on betahistine could not be separated according to indication. Over a 5-year period, total projected costs of cinnarizine for the treatment of tinnitus were CHF 0.8 million. The use of cinnarizine with dimenhydrinate for the treatment of vertigo resulted in cumulative net savings of CHF 1.2 million over a 5-year period.

7.1 Methodology costs, cost-effectiveness and budget impact

The systematic review was conducted following a review protocol, which is published on the FOPH website.[24]

7.1.1 Databases and search strategy

The economic systematic literature search followed the principles of the clinical systematic literature search, which is outlined in ***Section 6.1***. PubMed (MEDLINE), Embase.com and the Cochrane Library databases were searched for peer-reviewed scientific literature. In addition, the Tufts

Medical Centre Cost-Effectiveness Analysis (CEA) Registry (hereafter: the CEA Registry) and the international HTA database (both economic databases) were searched. The searches were built using the PICO reported in ***Chapter 4***. In PubMed (MEDLINE), Embase.com and the Cochrane Library, the search terms of the clinical systematic literature search were combined with cost-effectiveness search terms. The details of the search strategy are presented in ***Appendix F.***

All articles retrieved from PubMed (MEDLINE), Embase.com, the Cochrane Library, the CEA Registry and the international HTA database were reviewed in duplicate by 2 independent researchers in a similar manner to the systematic approach described in ***Section 6.1.3***, including firstly screening the title and abstract and subsequently screening the full text. In the first step, the major topics of the articles were assessed based on relevancy and articles that seemed to contain relevant data for the HTA objectives were selected for the full-text screening. If the 2 researchers disagreed on the relevance of an article, this was discussed. If the differences remained after discussion, the article was assessed in full text. Subsequently, the articles screened in full-text were assessed for inclusion based on pre-specified eligibility criteria (***Table 49***). Again any differences were resolved by discussion, and if needed a third researcher was consulted.

The process of selection of articles was recorded with Rayyan software (Rayyan Systems Inc., USA) and Endnote. The selection procedure applied during the full-text screening phase was reported in a PRISMA flow diagram and the primary reason for exclusion per article was listed in a table, like in the clinical approach.

Table 49. Inclusion and exclusion criteria for economic evaluation studies

	Inclusion criteria	Exclusion criteria
Publication year	All	None
Language of publication	English, French, German, Italian	All other languages
Country of study	Worldwide	None
Study design/ publication type	– Economic evaluations – Cost-utility analysis – Cost-effectiveness analysis – Cost-consequences analysis – Cost-minimisation analysis – Cost-benefit analysis – Budget impact analysis – Costing studies	– Resource use measurement – Irrelevant publication types (e.g. letter, comment, expert opinion, editorial, abstract only, conference presentation, book chapter and preprints)
Population	– Adult patients with Ménière's disease or Ménière's syndrome[a] – Adult patients with other peripheral or central vestibular disorders experiencing symptoms of vestibular vertigo (see Table 1)[b] – Adult patients with other peripheral or central vestibular disorders experiencing symptoms of tinnitus (see Table 1)[b]	– Animal studies – Patients aged <18 years – Patients who had already undergone destructive medical (e.g. intratympanic gentamicin) or surgical treatment (e.g. endolymphatic sac surgery, labyrinthectomy and vestibular neurectomy) – Other causes of vertigo (e.g. non-neurotological causes of vertigo, such as anxiety disorders or cardiac disease) – Other peripheral or central vestibular disorders which are out of scope for coverage for betahistine and cinnarizine with or without dimenhydrinate under the Swiss licensing because of other pathomechanisms[b]
Intervention	– Betahistine[c] – Cinnarizine[c] – Cinnarizine with dimenhydrinate[c]	Other interventions
Comparator	– Placebo[c] – No treatment[c]	– Other comparators – No comparator
Outcome	– Cost-effectiveness – Incremental/total healthcare costs – Life years and QALYs – ICER – Budget impact	– Studies with duplicate data (study with the largest sample size or most extended follow-up will be included for data extraction of the results)[d] – Unclear follow-up duration – Other outcomes

Abbreviations
ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years.
Notes
a = Although the term Ménière's syndrome is nowadays not often used, this term has been used formerly and therefore studies in patients with Ménière's syndrome were included.
b = Swiss clinical experts were consulted in order to check whether studies identified on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fell with-in the scope of the licensed indications of the interventions. Indications which were out of scope because of other pathomechanisms were excluded during the full-text selection with a documented reason for exclusion.
c = The interventions could also be evaluated together with co-interventions as long as these co-interventions are identical with those in the comparator arm.
d = If applicable, unique results from interim studies were included and interim studies were used as additional input on the study methodology.

7.1.2 Assessment of quality of evidence

The identified studies from the systematic literature search for cost-effectiveness were subjected to a critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, as recommended by current guidelines.[44,45] The CHEERS is a 28-item checklist with clear questions about the reporting of economic evaluations which gives insight into the general quality of the study.

7.1.3 Methodology data extraction and synthesis of health economic data

The following relevant data from the included articles found in the peer-reviewed literature were summarised using a data-extraction spreadsheet in Microsoft Excel:

– first author, year;

– country;

– type of study;

– study perspective;

– study funding;

– study population (sample size, mean age, age range and proportion men/women);

– intervention;

– comparator;

– outcome measures;

– total/incremental costs and quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs);

– model used (yes/no, type of model and health states);

– primary sources for the resource use/cost inputs;

– primary sources for the HRQoL inputs.

The data extraction spreadsheet was fully checked with the original articles by a second researcher. Data synthesis was done using descriptive comparisons of the study question, methods and results. Summary tables were included which present key information described in the data extraction. The ICERs were presented and the reliability (internal validity) and relevance (generalisability) of the estimates were explored. The analytical approaches used in the studies were compared and their robustness was discussed.

7.1.4 Cost-effectiveness analyses

Cost-effectiveness analyses were only performed for populations for which the clinical systematic literature search has shown that there is evidence for an effect of treatment. The data retrieved from the systematic review were synthesised for 4 populations of adult patients using betahistine or cinnarizine with or without dimenhydrinate experiencing symptoms of vertigo, tinnitus and hearing loss caused by Ménière's disease or other disorders. Only for cinnarizine with dimenhydrinate in patients with vertigo caused by other disorders than Ménière's disease evidence was found of a positive treatment effect compared to placebo (see ***Section 6.2.3.4***). As such, a cost-effectiveness analysis was conducted only for cinnarizine with dimenhydrinate in patients with vertigo caused by other disorders than Ménière's disease.

7.1.4.1 Target population

The population encompassed adult patients experiencing symptoms of vertigo caused by other disorders than Ménière's disease.

7.1.4.2 Setting and location

The analysis was performed for the Swiss healthcare setting. This means that, where possible, relevant input parameters were based on data from Switzerland, such as Swiss sources for healthcare use and associated costs.

7.1.4.3 Study perspective

The analysis was performed from a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government [i.e. federal government, cantons and communities], or out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

7.1.4.4 Intervention

The intervention of interest was cinnarizine with dimenhydrinate. Patients receive 3 combination tablets per day, each containing 20 mg cinnarizine and 40 mg dimenhydrinate. Tablets are administered orally.[38]

7.1.4.5 Comparator

Cinnarizine with dimenhydrinate was compared to no treatment.

7.1.4.6 Time horizon

Cinnarizine with dimenhydrinate is approved for treatment of vertigo for a maximum duration of 4 weeks in Switzerland.[46] Drug half-life is approximately 4 hours, implying that the effects of treatment would diminish quickly after treatment is discontinued. Therefore, a 4-week time horizon was used.

7.1.4.7 Discount rate

Given the short time horizon, discounting does not apply to the cost-effectiveness analysis.

7.1.4.8 Health outcomes

Health outcomes were reported in terms of reduction in mean vertigo score (MVS). The MVS is a composite outcome specifically developed for measuring the degree of vertigo and consists of 12 symptoms related to vertigo.[47] The MVS is usually expressed on a 5-point scale, ranging from 0

(no symptoms) to 4 (very strong symptoms). In some studies, alternative ranges of the MVS are used (e.g. in Otto et al 2008 the MVS ranges from 0 to 3).[37] The MVS was the primary endpoint in the study by Pytel et al 2007.[38] Pytel et al 2007 used a 5-point scale for MVS. A definition of the minimum clinically important difference (MCID) is lacking for MVS.

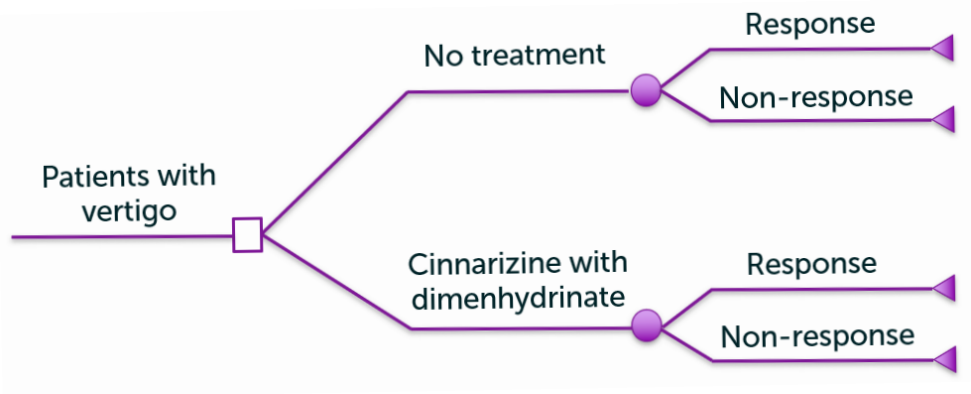
7.1.4.9 Currency, price data, and conversion

Costs were reported in Swiss Franc (CHF) in 2023 values. Price information was based primarily on Swiss sources. However, when necessary, costs were adjusted for inflation to 2023 price levels using inflation rates from the Swiss Federal Statistical Office.[48] Purchasing power parities were retrieved from the Organisation for Economic Co-operation and Development (OECD).[49]

7.1.4.10 Model structure

No studies evaluating the cost-effectiveness of cinnarizine with dimenhydrinate compared to no treatment for patients with vertigo were identified in the literature search for cost-effectiveness (see ***Section 7.2***). However, Stratmann et al 2006 developed a decision tree to compare costs of cinnarizine with dimenhydrinate to costs of betahistine in vertigo.[50] This study did not examine differences in QALYs, utilities or reduction in MVS, and no rationale was provided for not taking these effectiveness measures into account. Still, the decision tree provides a useful basis for a cost-effectiveness model. The conceptual model is illustrated in ***Figure 3***. The model was programmed in Microsoft Excel.

Figure 3. Conceptual model



7.1.4.11 Input parameters

The model input parameters on clinical outcomes were informed by the results of the data extraction of the clinical systematic literature search. Cost prices were based on the databases Spezialitätenliste, SASIS and TARMED.[51–53] Clinical experts were consulted whenever data were unavailable from the literature. An overview of the input parameters is provided in *Table 50*.

Table 50. Input parameters

Response rate			
Input parameter	**Value**	**Distribution in PSA**	**Source**
Cinnarizine with dimenhydrinate	83.6%	Beta (α=51; β=10)	Pytel et al 2007[38]
No treatment	46.6%	Beta (α=27; β=31)	Pytel et al 2007[38]
MVS scores			
Input parameter	**Value**	**Distribution in PSA**	**Source**
Baseline MVS	1.85	Not varied in PSA	Pytel et al 2007[38]
Effect cinnarizine with dimenhydrinate on MVS	-1.37	Normal (SD=0.66)	Pytel et al 2007[38]
Effect no treatment on MVS	-0.76	Normal (SD=0.48)	Pytel et al 2007[38]
Costs			
Input parameter	**Value**	**Distribution in PSA**	**Source**
Cinnarizine with dimenhydrinate acquisition cost 20 tablet package	CHF 9.75	Not varied in PSA	FOPH, Spezialitätenliste 2024[51]
Cinnarizine with dimenhydrinate acquisition cost 50 tablet package	CHF 25.35	Not varied in PSA	FOPH, Spezialitätenliste 2024[51]
Cinnarizine with dimenhydrinate acquisition cost 100 tablet package	CHF 39.75	Not varied in PSA	FOPH, Spezialitätenliste 2024[51]
Proportion of patients using 20 tablet package	18.6%	Dirichlet (n=3622; N=19513)	SASIS[52]
Proportion of patients using 50 tablet package	34.8%	Dirichlet (n=6792; N=19513)	SASIS[52]
Proportion of patients using 100 tablet package	46.6%	Dirichlet (n=9099; N=19513)	SASIS[52]
Cost of non-response	CHF 195.75	Gamma (α=25; β=7.83)	Stratmann et al 2006[50] and expert opinion

Abbreviations
CHF = Swiss Franc, FOPH = Federal Office of Public Health, MVS = mean vertigo score, PSA = probabilistic sensitivity analysis, SD = standard deviation.

7.1.4.11.1 Response rates and mean vertigo scores

Two studies on the effectiveness of cinnarizine with dimenhydrinate were identified in the clinical systematic literature search: Pytel et al 2007 and Otto et al 2008.[37,38] Both studies reported outcomes on the MVS, albeit on different outcome scales; MVS was reported on a 5-level scale (0-4) in Pytel et al 2007 and on a 4-level scale (0-3) in Otto et al 2008. For both outcome scales, scores of 0 indicate no symptoms and higher scores indicate more severe symptoms. The cost-effectiveness model was structured around treatment response. Only Pytel et al 2007 reported the proportion of patients that had a 50% reduction in MVS, which was considered as treatment response in the cost-effectiveness model. Since both studies used different outcome scales, the studies could not be pooled.

Table 51 presents response rates and mean MVS values after treatment for cinnarizine with dimenhydrinate and no treatment. The no treatment arm was informed by the placebo arm in the

study by Pytel et al 2007.[38] For no treatment, baseline MVS values were set equal to the baseline MVS values for patients receiving cinnarizine with dimenhydrinate.

Table 51. MVS at baseline, MSV after treatment and response rate stratified by treatment[a]

	Cinnarizine with dimenhydrinate	No treatment	Source
Baseline MVS	1.85	1.85[b]	Pytel et al 2007[38]
Response rate	83.6%	46.6%	Pytel et al 2007[38]
MVS after treatment	0.48	1.09	Pytel et al 2007[38]

Abbreviations
MVS = mean vertigo score.
Notes
a = MVS expressed on 0-4 scale, with higher scores indicating more severe symptoms.
b = Set equal to the baseline MVS for cinnarizine with dimenhydrinate group.

Values from the study by Pytel et al 2007 were used in the base case analysis since it reports on both response rates and MVS scores. In addition, the study by Pytel et al 2007 has a much larger study sample than Otto et al 2008. The study results from Otto et al 2008 were used in a scenario analysis. In the absence of response rates in Otto et al 2008, response rates from Pytel et al 2007 were used in this scenario analysis. MVS scores from Otto et al 2008 were rescaled to a 5-point scale to obtain outcomes that could be compared with the base case analysis.

The study by Pytel et al 2007 included patients with peripheral, central and combined central/peripheral vertigo.[38] According to the authors, this was done “to mirror the ’typical‘ vertigo patient seen in clinical practice”. Patients with BPPV were specifically excluded from participation in the study.[38] The authors did not provide a rationale for this exclusion criterion. As such, the results of the cost-effectiveness analysis might not be representative for patients with BPPV.

7.1.4.11.2 Death

Since vertigo does not affect life expectancy, mortality rates reflect those of the general population. As treatment with cinnarizine with dimenhydrinate did not affect life expectancy, mortality rates did not differ between cinnarizine with dimenhydrinate and no treatment. Given the short time horizon, combined with the relatively young age of the population as observed in the study by Pytel et al 2007 (i.e. 51.3 years[38]), death was not included in the model.

7.1.4.11.3 Adverse events

Both Pytel et al 2007 and Otto et al 2008 reported no significant differences in adverse events rates between both treatment arms.[37,38] Therefore, adverse events were not included in the base case analyses. A pragmatic search in non-randomised studies validated this assumption.

7.1.4.11.4 Acquisition costs of cinnarizine with dimenhydrinate

Cinnarizine with dimenhydrinate is available in 3 pack sizes, containing 20, 50 or 100 tablets. Prices of these packages in Switzerland (including value added tax) are provided in ***Table 52***. For a treatment period of 28 days and 3 tablets per day, 84 tablets are required. It was assumed that patients are provided with a single pack size (i.e. 5 packs of 20 tablets, 2 packs of 50 tablets or 1 pack of 100 tablets). Assuming that unused tablets are not redistributed to other patients, wastage was equal to 16 tablets, regardless of pack size. Since these tablets were assumed to remain unused, cost of wastage was included in the base case analysis.

Information on usage of different pack sizes in Switzerland were used to calculate the weighted average pack size (reported in ***Table 52***; derived from SASIS data). Acquisition costs of each pack size was derived from the Spezialitätenliste.[51] Based on this information, the average cost per tablet, including wastage was calculated (CHF 0.54; CHF 1.62 per day for 3 tablets). Scenario analyses were performed in which the average cost per tablet excluding wastage (CHF 0.45; CHF 1.36 per day) and the most economical option (i.e. pack size of 100 tablets) including wastage (CHF 0.47; CHF 1.42 per day) were used.

Table 52. Prices (including VAT) of different packages of cinnarizine with dimenhydrinate tablets

Pack size	Price[a]	Costs for 84 tablets, including wastage	Cost per tablet, including wastage	Cost per tablet, excluding wastage	Proportion of total packages
20 tablets	CHF 9.75	CHF 48.75 (5 packs)	CHF 0.58 (CHF 48.75 / 84)	CHF 0.49 (CHF 9.75 / 20)	18.6%
50 tablets	CHF 25.35	CHF 50.70 (2 packs)	CHF 0.60 (CHF 50.70 / 84)	CHF 0.51 (CHF 25.35 / 50)	34.8%
100 tablets	CHF 39.75	CHF 39.75 (1 pack)	CHF 0.47 (CHF 39.75 / 84)	CHF 0.40 (CHF 39.75 / 100)	46.6%

Abbreviations
CHF = Swiss Franc, VAT = value added tax.
Notes
a = Derived from Spezialitätenliste[51] (accessed 18 March 2024).

7.1.4.11.5 Healthcare costs

Since healthcare cost estimates could not be obtained from existing cost-effectiveness studies, additional pragmatic searches were performed to identify alternative sources for healthcare costs estimates for patients with vertigo, regardless of the treatment they receive. However, this did not result in additional information.

Stratmann et al 2006 assumed that treatment failure results in additional costs related to a visit to an otolaryngologist and treatment with medication other than cinnarizine with dimenhydrinate.[50] Costs for medication were based on the 3 most frequently described medications for vertigo, as reported by Hamann 2005.[54] In each of these medications, the active ingredient was betahistine. Since the clinical systematic literature search did not show that there is evidence for an effect of betahistine in vertigo, costs of medications with betahistine as active ingredient were not

incorporated in the model. As such, non-response was assumed to lead only to an additional visit to the otolaryngologist. The tariff of a healthcare visit is determined by the activities (in German: “Leistungen”) performed during the consult. The activities of a typical visit to the otolaryngologist were informed by expert opinion (n=3; average values were used). In combination with Swiss tariffs from TARMED, these activities were used to calculate the total cost of a single visit, equalling CHF 219.95 (***Table 53***).[53] A tax point value of 0.89 CHF was applied, based on Canton Zurich Government Council Resolution No. 857/2023, published on July 13, 2023. Using this tax point, the cost of a single visit is CHF 195.75. Clinical experts were asked to validate this. In a scenario analysis, 2 visits instead of a single visit to the otolaryngologist after non-response was used. Finally, a scenario analysis was performed in which non-response does not lead to an additional visit to the otolaryngologist.

Table 53. Costs related to a single visit

TARMED item	Activity	Taxpunkte AL[a]	Taxpunkte TL[a]	Volume[b]
00.0010	Consultation, first 5 minutes	10.42	8.19	1.00
00.0020	Consultation, each additional 5 min (patient age between 6 and 75 years)	10.42	8.19	2.13
00.0030	Consultation, last 5 minutes	5.21	4.10	1.00
00.0141	Patient dossier study	2.08	1.64	0.33
00.0610	Instructions to patient	10.42	8.19	0.07
00.2285	Report, up to 35 lines	22.90	18.03	1.00
00.2295	Report, additional 35 lines	18.74	14.75	0.07
08.1090	Video head impulse test	10.42	93.49	0.03
09.0610	Clinical vestibular examination with Frenzel glasses	45.81	51.81	1.00
09.0660	Quantitative measurement motor balance	15.68	68.33	0.07
Total (volume-weighted) costs per visit		*219.95*		

Abbreviations
CHF = Swiss Franc.
Notes
a = Derived from the TARMED browser (data accessed on March 15, 2024).
b = Based on expert opinion.

7.1.4.12 Base case analysis

The base case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections.

7.1.4.13 Scenario analyses

Scenario analyses were used to test the impact of assumptions in the model on the outcomes. ***Table 54*** shows the different scenario analyses, compared to the base case analysis.

Table 54. Scenario analyses

Health state transitions		
Parameter	**Base case**	**Scenario**
MVS scores	Pytel et al 2007[38]	Otto et al 2008[37]
Costs		
Parameter	**Base case**	**Scenario**
Costs of cinnarizine with dimenhydrinate	Average price, including wastage	– Lowest price, including wastage – Average price, excluding wastage
Costs of non-response	1 otolaryngologist visit	– 2 otolaryngologist visits – No otolaryngologist visits

Abbreviations
MVS = mean vertigo score.

7.1.4.14 One-way sensitivity analyses

Parameter uncertainty was first tested using one-way sensitivity analyses (OWSA) where model parameters were systematically and independently varied over plausible ranges. Standard deviations or standard errors were used for this purpose if reported in the study. If these data were unavailable, parameters were systematically varied by increasing and decreasing their values by 20% from the parameter value used in the base case. The ICER was recorded at the upper and lower limits to produce tornado diagrams.

7.1.4.15 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through a probabilistic sensitivity analysis (PSA) where all parameters to which probability distributions were assigned were varied jointly. The distributions that were applied in the PSA are provided in ***Table 50***. Monte Carlo simulations were performed in Microsoft Excel using Visual Basic for Applications (VBA), and the results were recorded. Results were plotted on the cost-effectiveness plane (CE plane). From these results, a cost-effectiveness acceptability curve (CEAC) was estimated.

7.1.5 Budget impact analyses

Three budget impact (BI) models were developed to assess the BI of betahistine, cinnarizine and cinnarizine with dimenhydrinate separately. The analyses were performed from the Swiss healthcare payer perspective. Costs were reported in CHF. The time horizon of the BI model was 5 years.

7.1.5.1.1 Data input

Data on the usage of betahistine, cinnarizine and cinnarizine with dimenhydrinate in the period between 2018 and 2022 were derived from SASIS database.[52] Data were available at an individual product level. SASIS database did not provide information on individual patients. Neither did SASIS

provide data on the indication for which products were used. These data were used in regression analyses to predict usage of individual products for the period 2024-2028. Total usage data were log-transformed, for better fitting regression analyses. Subsequently, the predicted usage of individual products was multiplied by 2023 Swiss prices (derived from the Spezialitätenliste), to predict total costs of medication for the period 2024-2028.[51]

7.1.5.1.2 Betahistine and cinnarizine without dimenhydrinate

For betahistine and cinnarizine without dimenhydrinate, no cost-effectiveness models were developed. The clinical systematic literature search showed that betahistine and cinnarizine without dimenhydrinate were not considered more effective than placebo, and did not have a different safety profile compared to placebo. Therefore, healthcare costs were assumed equal for betahistine or cinnarizine without dimenhydrinate compared to no treatment. The BI of betahistine and cinnarizine without dimenhydrinate was based only on the total costs of medication. For betahistine, data on multiple products were available (i.e. Betaserc, Betahistin-Mepha 24, Betahistin-Mepha 12 and Betahistin Spirig HC) in different dosages and pack sizes. For Betahistin Spirig HC, data were restricted for the period 2020-2022, since no costs were recorded prior to 2020. Betahistin Spirig HC was removed from the Spezialitätenliste in 2024. Therefore, the usage of Betahistin Spirig HC was not estimated using regression analyses. Instead, usage of different Betahistin Spirig HC packages in 2022 was assumed to remain constant in later years. Prices of alternative products with the same dose and pack size were used to value Betahistin Spirig HC products from in the budget impact analyses. For the various pack sizes Betahistin Spirig, utilisation data were not log-transformed, since ordinary least squares regressions showed better fit for the various pack sizes of this product. For cinnarizine, data were available for one product only (i.e. cinnageron), available in 2 pack sizes. SASIS did not provide data on numbers of patients using betahistine and cinnarizine without dimenhydrinate. Since treatment duration for betahistine and cinnarizine without dimenhydrinate was unknown and potentially variable between patients, it was not possible to estimate numbers of patients using these treatments.

7.1.5.1.3 Cinnarizine with dimenhydrinate

The BI for cinnarizine with dimenhydrinate consisted of medication costs and cost related to healthcare use. For cinnarizine with dimenhydrinate, only one product was available (i.e. Arlevert), available in 3 pack sizes. Data from SASIS were used to predict the total costs of medication for the period 2024-2028 using regression analyses.[52] Cinnarizine with dimenhydrinate was licensed for treatment of transient vertigo without specification of the underlying cause. SASIS did not provide data on the indication for which patients used cinnarizine with dimenhydrinate. Experts were therefore consulted to provide an estimate. One expert estimated that in the general Swiss population 4.5% of patients used cinnarizine with dimenhydrinate for vertigo caused by Ménière's disease and 95.5% for transient vertigo caused by other disorders than Ménière's disease. According to this expert, this was a rough estimate since exact data were missing. Two experts stated that in

the university hospital setting, approximately 75% of cinnarizine with dimenhydrinate was used to treat vertigo caused by Ménière's disease and 25% for transient vertigo caused by other disorders. However, the patient population treated in the hospital might deviate from the general population in Switzerland. Therefore, the estimates provided for the general Swiss population were used in the BI analysis. To acknowledge the uncertainty surrounding the estimates, a scenario was run in which it was assumed that the use of cinnarizine with dimenhydrinate was divided equally over vertigo caused by Ménière's disease and vertigo caused by other disorders.

In the cost-effectiveness model, cinnarizine with dimenhydrinate was assumed to lead to a reduction in healthcare use, compared to no treatment for patients with vertigo caused by other disorders than Ménière's disease. For this population, per-patient costs related to healthcare consumption for the BI model were derived from the cost-effectiveness model. These costs were multiplied by the number of people using cinnarizine with dimenhydrinate for vertigo caused by other disorders than Ménière's disease in Switzerland, which were calculated based on data from SASIS.[52]

Healthcare costs were assumed equal for cinnarizine with dimenhydrinate compared to placebo for patients using medication for treatment of vertigo caused by Ménière's disease. The BI of cinnarizine with dimenhydrinate for patients using medication for treatment of vertigo caused by Ménière's disease was therefore based only on the total costs of medication.

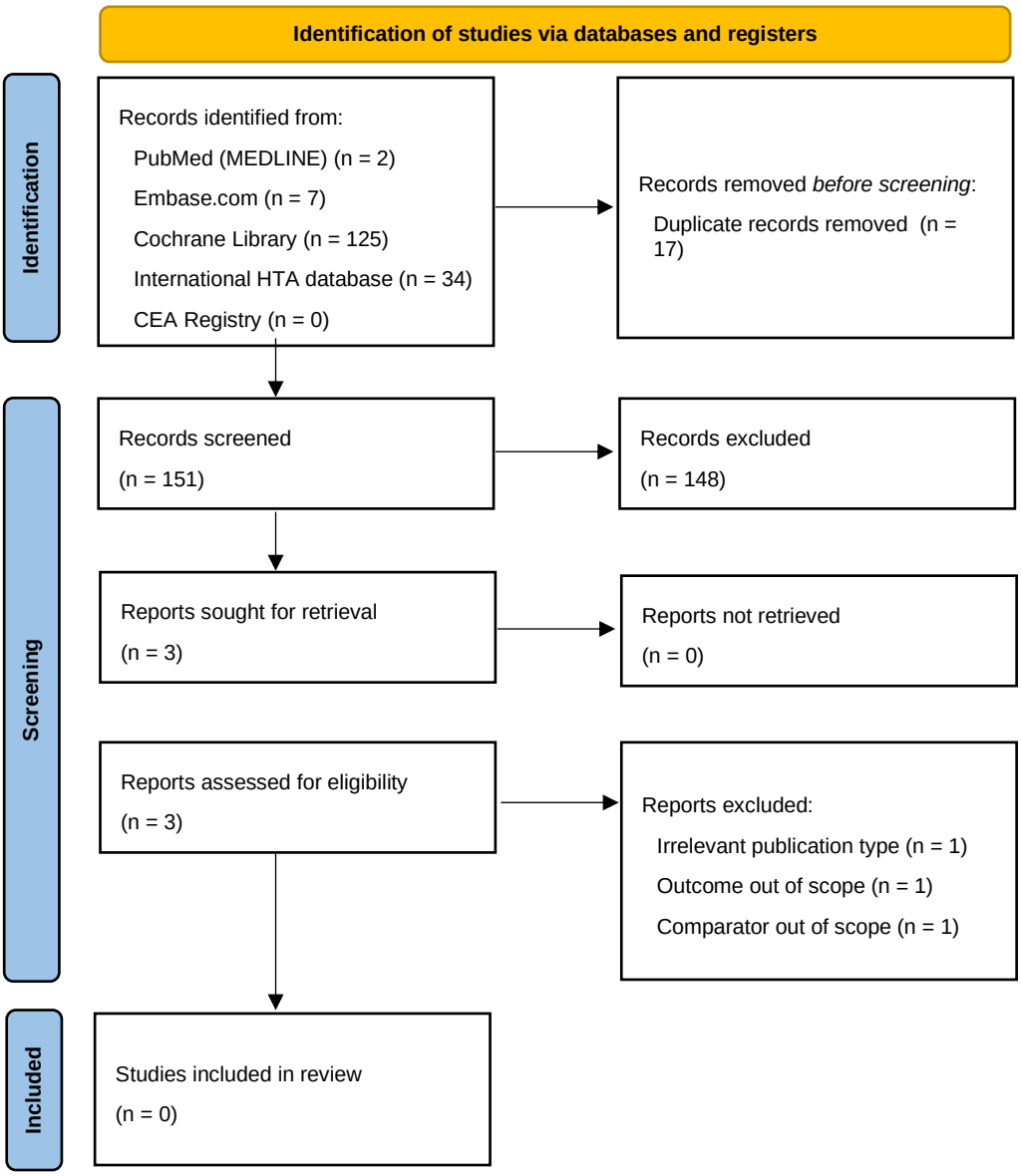
SASIS did not provide data on numbers of patients using cinnarizine with dimenhydrinate but patient numbers could be calculated since treatment duration was assumed 28 days (equal to Swiss licensing) and different pack sizes. The BI is calculated as the difference between the total costs (i.e. medication costs and cost of healthcare use) of both treatment strategies for the total population of patients being treated with cinnarizine with dimenhydrinate.

7.2 Results costs, cost-effectiveness and budget impact

7.2.1 PRISMA flow diagram

The results of the primary systematic literature search for cost-effectiveness are summarised in ***Figure 4.*** On 14 November 2023, a total of 151 unique records were identified in PubMed (MEDLINE), Embase.com, the Cochrane Library and the international HTA database. Of these records, 148 records were excluded based on title and abstract. The 3 articles selected for full-text screening were all excluded due to the following reasons: wrong publication type, outcome out of scope and comparator out of scope. More details regarding these articles are provided in ***Appendix G.*** . No studies were identified during the additional systematic literature search conducted on 29 January 2024 in PubMed (MEDLINE), Embase.com and the Cochrane Library, and on 6 February 2024 in the CEA Registry and the international HTA database.

Figure 4. PRISMA flow diagram of the economic systematic literature search[a]



Abbreviations
CEA = cost-effectiveness analysis, HTA = health technology assessment, PRISMA = Preferred Items for Systematic Reviews and Meta-Analyses.
Notes
a = Search date 14 November 2023.

7.2.2 Findings costs

Acquisition costs of betahistine and cinnarizine with or without dimenhydrinate were derived from the Spezialitätenliste and are provided in ***Table 55***.[51]

Table 55. Acquisition costs for betahistine, cinnarizine with or without dimenhydrinate

Betahistine	
Medication name	**Acquisition costs (CHF)[a]**
Betahistin-Mepha 16 – 50 tablets	9.00
Betahistin-Mepha 16 – 100 tablets	16.10
Betahistin-Mepha 24 – 50 tablets	15.75
Betahistin-Mepha 24 – 100 tablets	34.60
Betaserc 8 mg – 50 tablets	8.35
Betaserc 8 mg – 100 tablets	15.65
Betaserc 16 mg – 50 tablets	9.30
Betaserc 16 mg – 100 tablets	17.40
Betaserc 24 mg – 50 tablets	18.85
Betaserc 24 mg – 100 tablets	36.60
Cinnarizine	
Medication name	**Acquisition costs (CHF)[a]**
Cinnageron 30	15.55
Cinnageron 100	38.25
Cinnarizine with dimenhydrinate	
Medication name	**Acquisition costs (CHF)[a]**
Arlevert 20 tablets	9.75
Arlevert 50 tablets	25.35
Arlevert 100 tablets	39.75

Abbreviations
CHF = Swiss Franc.
Notes
a = Derived from Spezialitätenliste[51] (accessed 18 March 2024).

As described in ***Section 7.1.4***, the included studies did not provide relevant healthcare cost data for the Swiss cost-effectiveness and BI models, except for the assumption in Stratmann et al 2006 that non-response to treatment would lead to an additional visit to the otolaryngologist.[50] Clinical experts were asked to provide details on the activities list during such an additional visit. Swiss databases and publicly available sources were used for the unit costs of the activities. ***Table 53*** provides the unit costs.

7.2.3 Findings cost-effectiveness

The base case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. ***Table 56*** shows the total costs and effects and incremental costs and effects of cinnarizine with dimenhydrinate compared with no treatment. Cinnarizine with dimenhydrinate resulted in additional effects, at lower costs. Consequently, cinnarizine with dimenhydrinate was the dominant treatment strategy.

Table 56. Costs, effects and corresponding incremental costs and effects

Treatment	Costs (CHF)	Effects (MVS)	Incremental costs (CHF)	Incremental effects	ICER Cost per MVS point reduced
No treatment	105	1.09			
Cinnarizine with dimenhydrinate	77	0.48	-27	0.61	Cinnarizine with dimenhydrinate dominates

Abbreviations
CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, MVS = mean vertigo score.

7.2.3.1 Scenario analyses

Six scenario analyses were run, adjusting for different parameters. The results are presented in ***Table 57***. Cinnarizine with dimenhydrinate dominated no treatment, except in two scenarios. Only when the costs of an ENT visit due to non-response were completely ignored (i.e. assuming no additional ENT visits due to non-response), a positive ICER was estimated, but was still below CHF 100 per MVS point reduced.

Table 57. Outcomes scenario analyses cost-effectiveness

Treatment	Incremental costs (CHF)	Incremental effects	ICER Cost per MVS point reduced (CHF)
Base case	-27	0.61	Cinnarizine with dimenhydrinate dominates
MVS scores from Otto et al[37]	-27	1.31	Cinnarizine with dimenhydrinate dominates
Cost of wastage excluded	-34	0.61	Cinnarizine with dimenhydrinate dominates
Lowest acquisition costs	-33	0.61	Cinnarizine with dimenhydrinate dominates
Two ENT visits in case of non-response	-100	0.61	Cinnarizine with dimenhydrinate dominates
No additional ENT visits in case of non-response	45	0.61	74

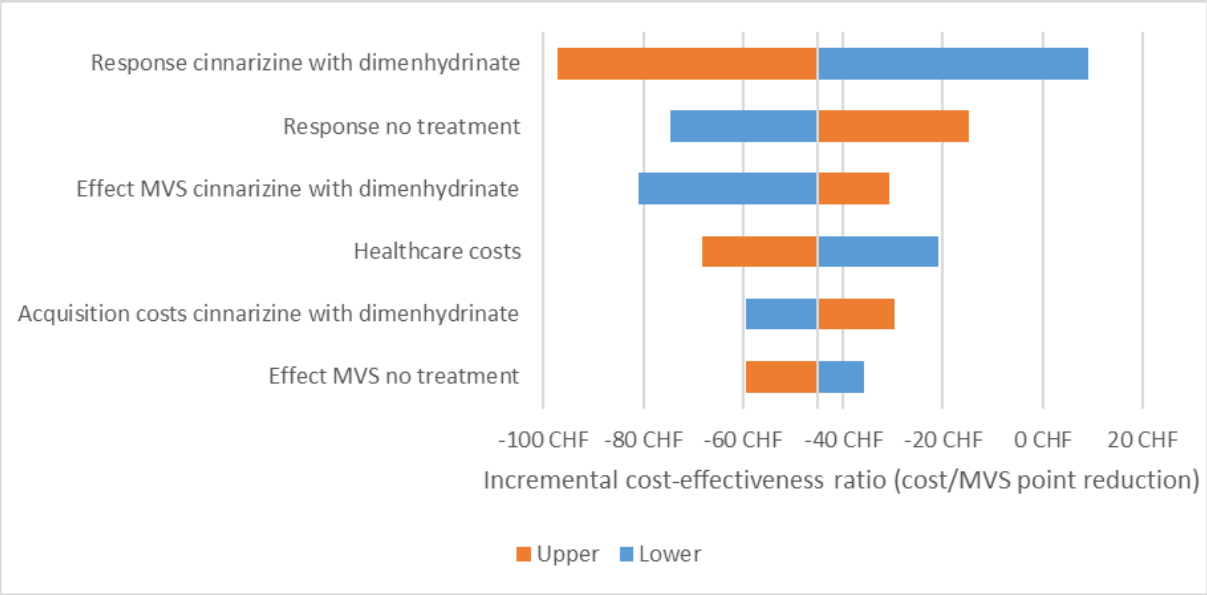
Abbreviations
CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, MVS = mean vertigo score.

7.2.3.2 One-way sensitivity analyses

Figure 5 presents the tornado diagram of the OWSA. The width of the bars represents the potential range of the estimate given the potential variation in each variable with the other variables held constant. As indicated by their order (highest impact on top), the parameters with the largest impact

on the ICER were the response rates, especially for cinnarizine with dimenhydrinate. Using the lower value of the response rate for cinnarizine with dimenhydrinate (i.e. response rate of 0.669) resulted in an ICER of CHF 9 per MVS point reduction. All other OWSAs resulted in dominant ICERs for both upper and lower values.

Figure 5. Tornado diagram of One-Way Sensitivity Analysis

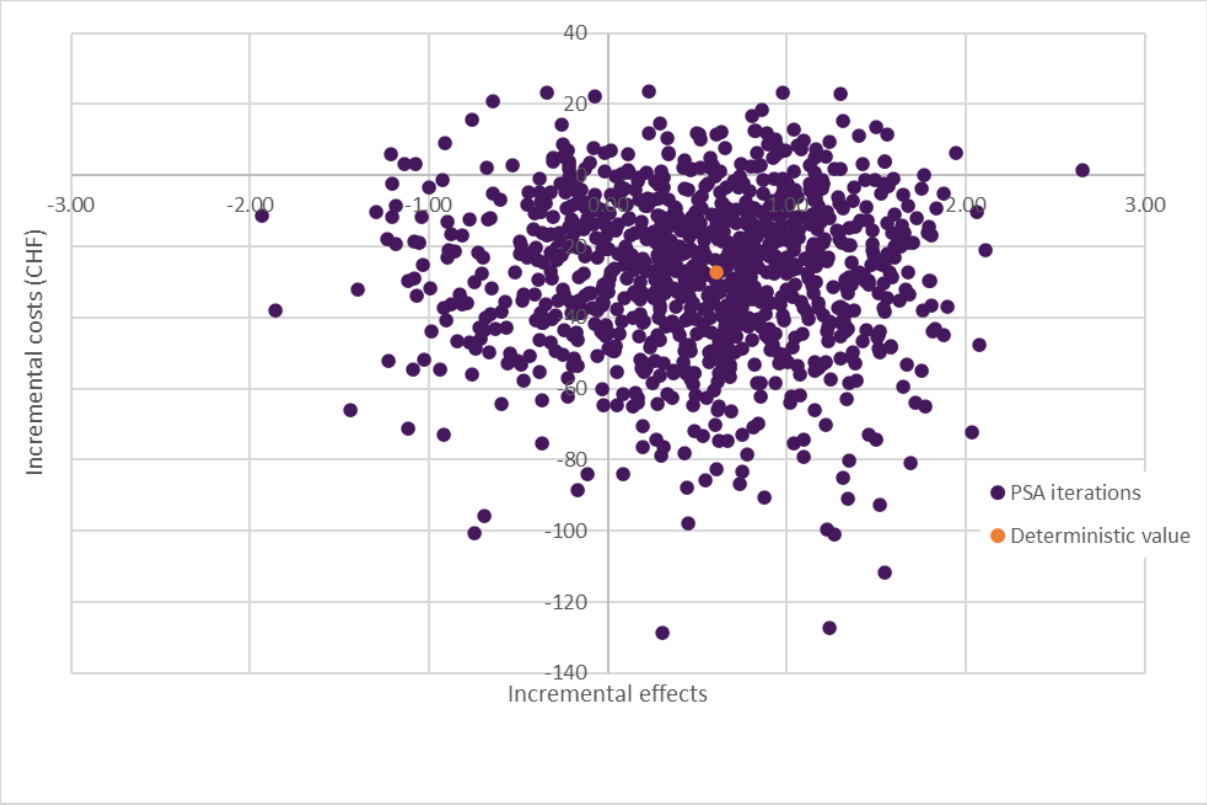


Abbreviations
CHF = Swiss franc, MVS = mean vertigo score.

7.2.3.3 Probabilistic sensitivity analysis

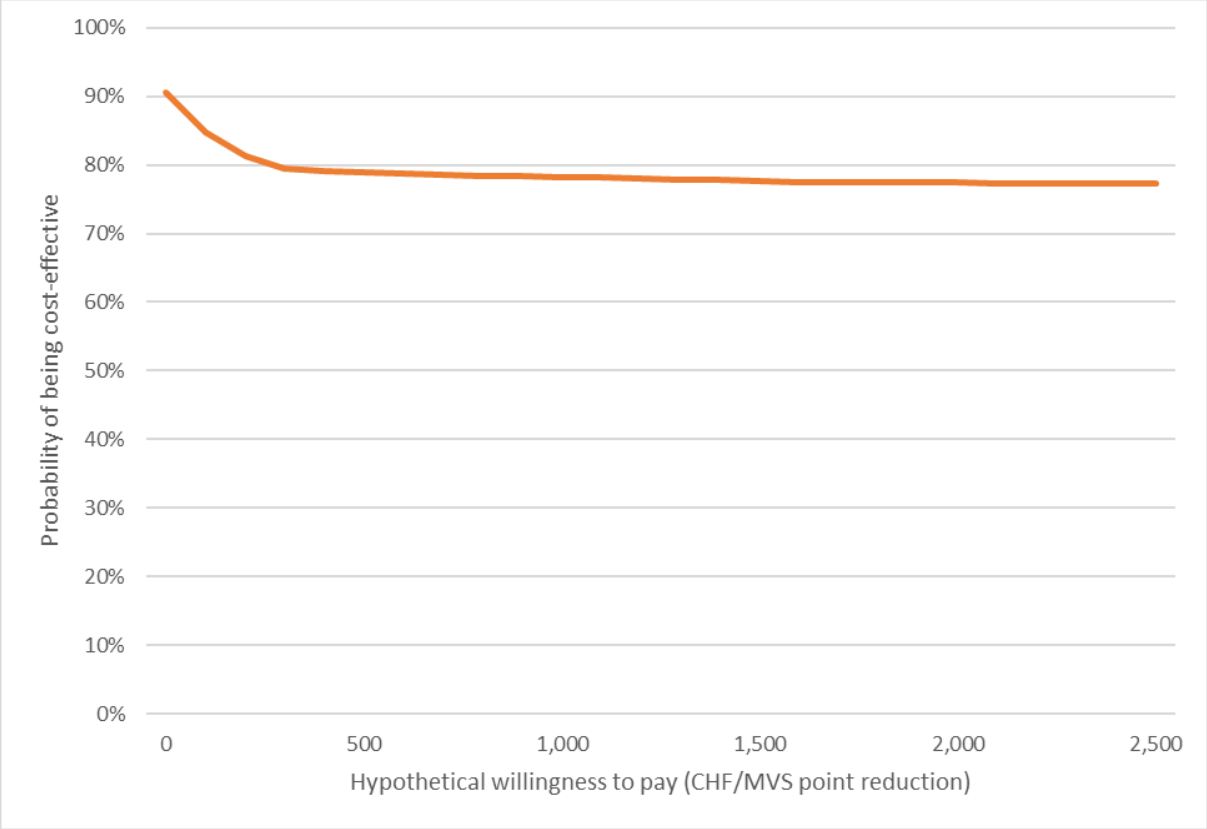
Cost-effectiveness planes (CE-planes) and cost-effectiveness acceptability curves (CEAC) are presented in ***Figure 6*** and ***Figure 7***. The PSA presents findings similar to those of the deterministic analyses. The vast majority of PSA iterations (91%) were located in the bottom section of the CE-plane, meaning costs savings for cinnarizine with dimenhydrinate compared to no treatment. The majority of iterations (70%) are in the south-east quadrant of the CE-plane, meaning that cinnarizine with dimenhydrinate is dominant (more effective and lower costs) over no treatment. Reviewing the CEAC in ***Figure 7***, the probability of cinnarizine with dimenhydrinate being optimal is 91% at a threshold of CHF 0, equal to the proportion of iterations being cost saving. At a hypothetical willingness to pay threshold of approximately CHF 300, 79% of PSA iterations would be considered cost-effective. The acceptability curve plateaus at a threshold of CHF 2000, when approximately 77% of iterations being cost-effective.

Figure 6. Cost-effectiveness plane



Abbreviations
CHF = Swiss franc, PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year.

Figure 7. Cost-effectiveness acceptability curve



Abbreviations
CHF = Swiss franc, MVS = mean vertigo score.

7.2.4 Findings budget impact

7.2.4.1 Betahistine and cinnarizine without dimenhydrinate

The BI of betahistine and cinnarizine without dimenhydrinate compared to no treatment over a period of 5 years is presented in ***Table 58***. Data from SASIS showed that, over the period between 2018-2022, the average number of reimbursed packages of betahistine was about 165,000 per year. Using 2023 prices, the yearly cost of betahistine usage in this period was CHF 3.2 million. Over a 5-year period, total projected costs of betahistine were CHF 17.2 million.

Data from SASIS showed that the number of reimbursed packages of cinnarizine was decreasing consistently over the period 2018-2022. In 2018, more than 11,000 packages of cinnarizine were registered, decreasing to less than 8,000 packages in 2022. Likewise, costs associated with cinnarizine also decreased over the years. In 2024, projected costs of cinnarizine were CHF 183,586. Over a 5-year period, total projected costs of cinnarizine were CHF 0.8 million.

Table 58. Annual and cumulative BI (CHF) of betahistine and cinnarizine without dimenhydrinate, 5-year period

Treatment	2024	2025	2026	2027	2028	Cumulative BI
Betahistine	3,359,786	3,396,129	3,436,721	3,481,609	3,530,847	17,205,092
Cinnarizine	183,586	167,930	153,614	140,522	128,550	774,202

Abbreviations
BI = budget impact, CHF = Swiss Franc.

7.2.4.2 Cinnarizine with dimenhydrinate

Data from SASIS showed that, number of packages of cinnarizine with dimenhydrinate was relatively stable between 23,000 and 27,000 packages over the period 2018-2022, albeit there was a slight decrease from 2018 onwards. Based on package size and label dose, the estimated number of patients in Switzerland using cinnarizine with dimenhydrinate varied between 10,683 (2024) and 9,728 (2028). It was assumed that 4.5% of patients used cinnarizine with dimenhydrinate for vertigo caused by Ménière's disease and 95.5% for transient vertigo caused by other disorders than Ménière's disease.

Yearly costs of cinnarizine with dimenhydrinate use decreased accordingly. ***Table 59*** shows that for the total population, the use of cinnarizine with dimenhydrinate resulted in a budget savings of CHF 0.2 million per year on average. Cumulative budget saving over a 5-year period was CHF 1.2 million. ***Table 59*** also shows that the budget saving was explained by savings on the treatment of vertigo caused by other disorders than Ménière's disease (explained by lower healthcare costs compensating for increased cost of medication use).

Table 59. Annual and cumulative costs and BI (CHF) of cinnarizine with dimenhydrinate, 5-year period

Treatment	2024	2025	2026	2027	2028	Cumulative
Total population						
Cinnarizine with dimenhydrinate	807,906	789,343	771,222	753,532	736,263	3,858,265
Standard of care	1,066,470	1,041,747	1,017,617	994,066	971,078	5,090,979
BI	-258,564	-252,404	-246,396	-240,534	-234,816	-1,232,714
Patients using cinnarizine with dimenhydrinate for the treatment of vertigo caused by Ménière's disease						
Cinnarizine with dimenhydrinate	21,617	21,123	20,641	20,171	19,711	103,263
Standard of care	0	0	0	0	0	0
BI	21,617	21,123	20,641	20,171	19,711	103,263
Patients using cinnarizine with dimenhydrinate for the treatment of vertigo caused by other disorders than Ménière's disease						
Cinnarizine with dimenhydrinate	786,289	768,219	750,580	733,361	716,552	3,755,001
Standard of care	1,066,470	1,041,747	1,017,617	994,066	971,078	5,090,979
BI	-280,181	-273,528	-267,037	-260,705	-254,527	-1,335,977

Abbreviations
BI = budget impact, CHF = Swiss Franc.

Table 60 presents total costs and disaggregated costs of cinnarizine with dimenhydrinate compared to standard of care. ***Table 60*** shows that the savings on healthcare costs compensate for the acquisition costs of cinnarizine with dimenhydrinate. Costs of cinnarizine with dimenhydrinate medication in the period 2024-2028 was projected to be CHF 2.3 million (yearly projected costs decreasing from CHF 0.5 million in 2024 to CHF 0.4 million in 2028). These costs were offset by savings in healthcare costs, due to the higher response rate of cinnarizine with dimenhydrinate compared to no treatment for patients using cinnarizine with dimenhydrinate for the treatment of vertigo caused by other disorders than Ménière's disease. On a yearly basis, savings on healthcare consumption amount to around CHF 0.7 million in this patient population.

Table 60. Breakdown of cumulative BI (CHF) of cinnarizine with dimenhydrinate, 5-year period

	Cinnarizine with dimenhydrinate	Standard of care	BI
Total costs 2024-2028	3,858,265	5,090,979	-1,232,714
Costs of cinnarizine with dimenhydrinate	2,294,743	0	2,294,743
Healthcare costs	1,563,522	5,090,979	-3,527,457

Abbreviations
BI = budget impact, CHF = Swiss Franc.

In a scenario, it was assumed that the 50% of cinnarizine with dimenhydrinate was used to treat vertigo caused by Ménière's disease and 50% was used for transient vertigo caused by other disorders than Ménière's disease, to accommodate the uncertainty around the cause of vertigo. In

this scenario, reduced healthcare costs did not compensate the increased costs of medication, leading to a cumulative positive budget impact of CHF 0.4 million over a 5-year period.

8. Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

The systematic reviews on efficacy, effectiveness, safety, and cost-effectiveness and additional pragmatic searches identified 24 publications concerning ethical, social, and organisational issues associated with the treatment of Ménière's disease, vertigo and tinnitus. Ethical issues concerned the challenges in diagnosing and treating Ménière's disease, vertigo and tinnitus, which extend beyond their physical manifestations and can significantly influence an individual's quality of life, mental health and social interactions. Driving restrictions for patients with Ménière's disease and vertigo were considered as legal issues. Social issues discussed in the literature considered the impact Ménière's disease, vertigo and tinnitus can have on a patient's social network and society as a whole. The need for a holistic approach as advocated in the literature requires input from various healthcare professionals, potentially complicating the organisation of treatment pathways, was considered a potential organisational issue.

8.1 Methodology ethical, legal, social and organisational issues

8.1.1 Databases and search strategy

The full texts of studies identified for evaluating the ethical, legal, social, and organisational (ELSO) issues encountered during the systematic reviews on efficacy, effectiveness, safety, and cost-effectiveness were reviewed. Additionally, grey literature on the ELSO issues was searched on relevant websites, including those of the AAO-HNS, the Bárány Society, and patient organisations such as www.menieres.org.uk and www.vestibular.org. Lastly, a pragmatic search was conducted to ensure comprehensive coverage of the ELSO issues.

8.1.2 Other sources

Not applicable.

8.1.3 Assessment of quality of evidence

Not applicable.

8.1.4 Methodology data extraction, analysis and synthesis of the domains ethical, legal, social and organisational issues

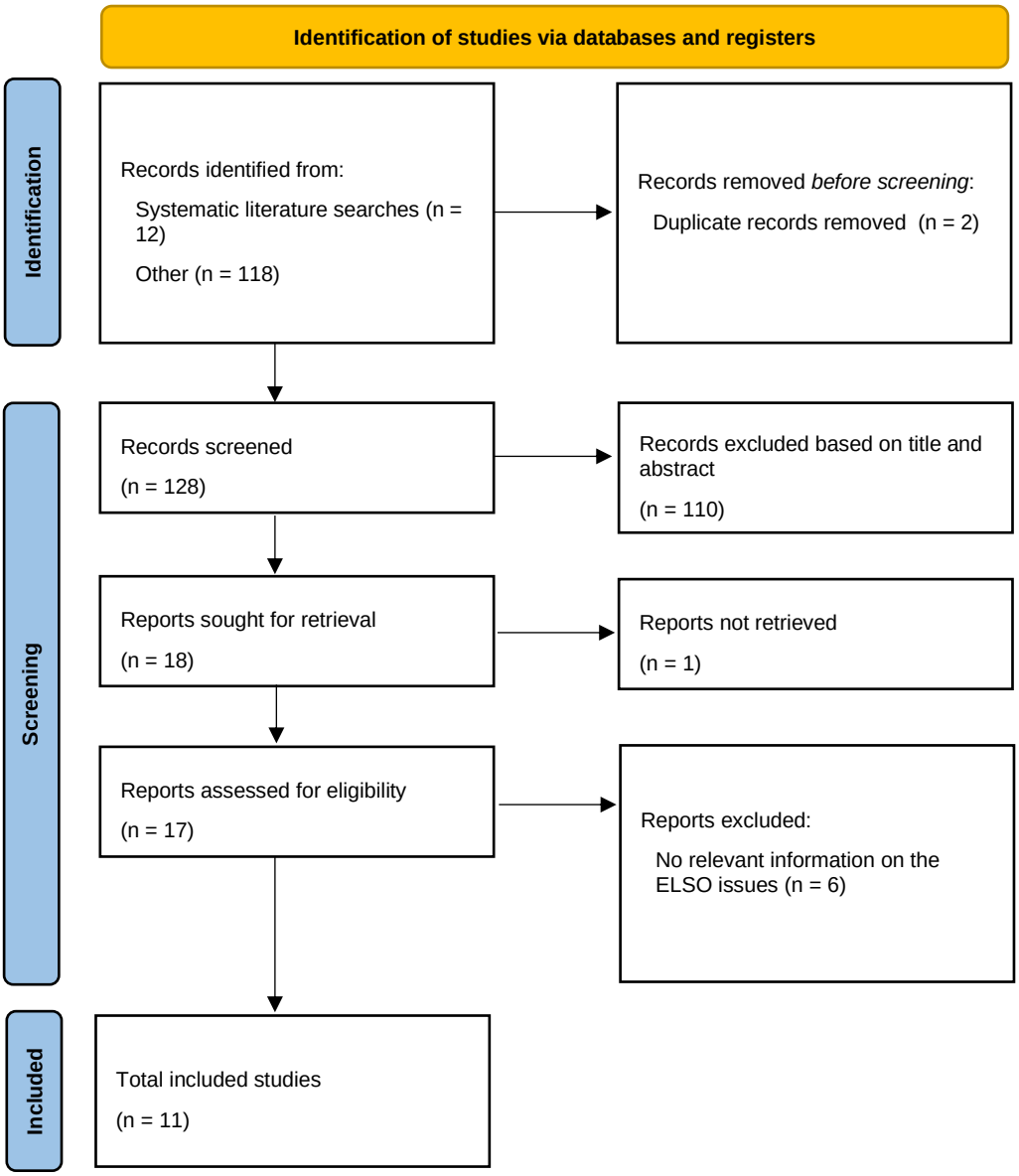
The summary of the findings related to the ELSO issues was provided narratively. No statistical tests were applied to the literature search output of these domains.

8.2 Results ethical, legal, social and organisational issues

8.2.1 PRISMA flow diagram

The results of the literature search on ELSO issues are summarised in ***Figure 8***. In total, 128 unique records were identified for the systematic literature search and other sources with the search on 12 February 2024. Of those, 110 records were excluded based on title and abstract, one record was excluded because it could not be retrieved, leaving 17 articles for review in full-text. A total of 11 articles were included in the systematic review. For all excluded articles, the reason for exclusion was that no relevant information was identified in the full-text review.

Figure 8. PRISMA flow diagram of the literature search for the ELSO issues[a]



Abbreviations
ELSO = ethical, legal, social, and organisational, PRISMA = Preferred Items for Systematic Reviews and Meta-Analyses.
Notes
a = Search date 12 February 2024.

After expert input during the review phase of the HTA report, 10 additional studies were identified as relevant and added to the ELSO domains.

8.2.2 Study characteristics and risk of bias of included studies

Not applicable.

8.2.3 Evidence table

Not applicable.

8.2.4 Findings ethical issues

This section discusses the significant challenges and ethical considerations in accurately diagnosing and treating Ménière's disease, highlighting issues such as diagnostic delays, the complexity of symptoms, and the uncertainty around the efficacy of commonly prescribed medications.

8.2.4.1 Diagnosis

The challenge of accurately diagnosing Ménière's disease or syndrome has been described in several studies.[53,54] Diagnostic delays often occur because Ménière's disease presents with non-specific clinical manifestations during its initial stages, before patients are referred to specialists.[56] The coexistence of Ménière's disease and vestibular migraine and overlapping symptoms in the two disorders complicate their differentiation.[57,58] The disease's inherent heterogeneity and variability in occurrence and latency of symptoms complicates the diagnostic process, with only 38% of patients receiving an initial correct diagnosis and on the other hand some patients diagnosed with Ménière's may not undergo evaluations for alternative conditions, further complicating the diagnostic process.[57,58] This complexity leads to misdiagnoses, as the absence of a definitive diagnostic test for Ménière's syndrome often results in confusion between symptoms of dizziness and vertigo.[60] MRI hydrops sequences and electrocochleography may increase diagnostic certainty, but these tests have not yet been adopted in diagnostic criteria.[61] Several authors emphasized the need for a more thorough evaluation in diagnosing Ménière's disease, arguing that the lack of a definitive diagnostic test contributes significantly to the high incidence of misdiagnoses, where vertigo symptoms are often misinterpreted.[60,62–64] This complex diagnostic landscape not only results in missed Ménière's diagnoses but also subjects those diagnosed with Ménière's to potential oversight of other medical conditions.[62–64]

Recent studies on the experiences of dizzy patients indicate that Ménière's syndrome is often diagnosed when doctors encounter vertigo without a clear understanding of the underlying cause.[62–64] Ethical concerns were raised regarding prescribing lifelong drug regimens in the absence of a

concrete diagnostic method, highlighting issues related to patient well-being and the responsibilities of healthcare professionals.[65] Swiss experts indicated that in Switzerland, this issue might not be prominent, since medication is stopped in patients with longer attack-free intervals. Misdiagnosis can result in delayed or inappropriate treatment, potentially leading to disease progression, reduced quality of life and a financial burden to individuals and society.[66] According to Chen et al 2023, Ménière's disease requires specific management strategies tailored to its symptoms, making a correct diagnosis crucial. Furthermore, administering medications or interventions unsuitable for Ménière's may lead to ineffective symptom control, impacting an individual's quality of life.

Several ethical constraints arise from misdiagnosis, encompassing delayed treatment, ineffective symptom management, reduced quality of life, psychological distress, financial burden, strain on the patient-physician relationship, and missed opportunities for early intervention.[57,59,60]

8.2.5 Findings legal issues

In Switzerland, drugs can only be placed on the Spezialitätenliste if drugs are licensed by Swissmedic and are effective, appropriate, and economically efficient. Currently, the licensing of betahistine, cinnarizine and cinnarizine with dimenhydrinate is not limited.

Huppert et al 2018 discussed that driving restrictions for patients with Ménière's disease and patients with vertigo vary considerably in Europe.[67] In particular, the authors claim that the Swiss regulations leave room for clinical interpretation. Patients with balance disturbances are not allowed to drive, but when a patient with Ménière's disease has no vertigo, they are typically allowed to drive. In a cross-sectional study in Finland, it was found that people with Ménière's disease were at lower risk of traffic incidents than the general population.[68] The authors claim that this might be explained by selective driving.

8.2.6 Findings social issues

In the following section, the impact that Ménière's disease, vertigo, and tinnitus have on patients' physical, psychological, and social well-being are being discussed, highlighting the associated challenges and the necessity for comprehensive support systems.

8.2.6.1 Quality of life

In the UK, patients with Ménière's disease showed reduced HRQoL compared to the general population, facing notable difficulties in fulfilling work and social roles. The study by Yardley et al 2003 indicates that vertigo has the most significant impact on patients' quality of life (as measured with SF-36), with additional factors such as ear pressure, hearing loss, and tinnitus also contributing to poorer outcomes.[69] Patients with Ménière's disease scored lower than the general population without long-term health problems on all domains of the SF-36. Compared to the general population with long-term health problems, patients with Ménière's disease had similar scores on most

domains of quality of life. On physical and emotional domains, patients with Ménière's disease suffered more problems than the persons in the general population with long-term health problems. The study of Tyrell et al 2016 further highlights that the negative impact on patients' emotional and psychological well-being compromises their overall quality of life.[70] Anderson et al 2001 found that quality of well-being scores were 44% lower for patients with Ménière's disease than for people with no symptoms and full functional status.[71] Patients with Ménière's disease had a SF-12 physical score of 38.9 and a SF-12 mental score of 44.2, compared to general population mean scores of 50.

8.2.6.2 Depressive symptoms

Diseases of the peripheral vestibular system, such as Ménière's disease and BPPV, significantly impact patients' physical and psychological well-being. Several studies highlight a high prevalence of depressive symptoms among these patients.[65,72–79] The high prevalence of anxiety and depression among these patients, exacerbated by the unpredictability of vertigo attacks, leading to self-restricting behaviour and diminished quality of life.[62,66,68] The bidirectional relationship between Ménière's disease and depression raises concerns about the compounded impact on mental health.[80]

8.2.6.3 Societal impact of disease

A German study reported a 1-year prevalence of vestibular vertigo in 5% of adults, with 80% experiencing medical consultations, interference with daily activities, or work absences.[81] Coping with depression due to Ménière's disease requires significant financial and emotional resources, affecting both the patients and their support networks.[82] The economic burden is evident during vertigo attacks, causing increased medical expenses and disruptions in work and daily activities.[70]

8.2.6.4 Social isolation

Ménière's disease, along with vertigo and tinnitus, significantly impacts a person's personal and social life.[82] Patients often experience embarrassment and perceive themselves as displaying socially undesirable behaviour during an attack, which can lead to social isolation. This isolation, in turn, triggers anxiety and social phobias.[68,71] The repetition and severity of attacks can lead to psychiatric repercussions of a panic-phobic nature.[83] In patients with Ménière's disease, the frequent episodes of dizziness can lead to a reactive behaviour where they start avoiding places or situations, eventually developing agoraphobia.

8.2.6.5 Impact on social networks

The emotional and psychological toll of Ménière's disease further emphasizes the need for psychological support for individuals dealing with the condition.[69] The study of Talewar et al 2020 aimed to explore the meanings of Ménière's disease from the perspective of those living with it,

focusing on what was significant and important in their everyday lives.[82] Participants described the disease as highly disruptive, impacting not only their everyday routines but also key family events and relationships. Participation restrictions were also observed in a Finnish study among 500 respondents with Ménière's disease.[84] The condition was seen as intrusive, with enduring effects on various facets of their lives, including personal, social, cultural, and professional domains. This disruption led to lowered expectations regarding their capacity to live life and participate in family activities as they had once hoped. Although planning contingencies to avoid or manage attacks offered some sense of control, the psychosocial costs for these individuals were considerable. According to Tyrell et al 2016, the significance of friends and family becomes paramount in mitigating the social consequences of Ménière's disease.[70] This underscores the need for holistic care and understanding to address the complex challenges associated with the condition. The authors further emphasized the value of support networks in helping patients lead satisfying lives despite the isolation, fear, and dependency they often feel. Stephens et al 2012 also found a wide range of effects of Ménière's disease on patients' significant others, including participation restrictions and uncertainty.[85]

8.2.7 Findings organisational issues

The diagnostic and treatment challenges for Ménière's disease, along with vertigo and tinnitus, has been argued to necessitate a holistic, patient-centred approach. According to Tassinari et al 2015, individualized treatment is essential due to frequent misdiagnoses and varied treatment efficacy, making disease management difficult.[86] Nevoux et al 2018 highlights the variation in treatment between centres, emphasizing the need for personalized care. They argue that lifestyle adjustments and psychotherapy are crucial for a holistic approach that considers the patient's social and psychological aspects.[12]

These complexities require input from various healthcare professionals, potentially complicating the organisation of treatment pathways and stressing the importance of patient preferences in decision-making.

9. Additional issues

9.1 Guideline recommendations

9.1.1 Ménière's disease

Because the underlying cause of Ménière's disease is not fully understood, managing the disease is inherently challenging and solely focused on reducing symptoms, as outlined in the clinical practice guideline developed by AAO-HNS. The aim of the treatment is primarily to reduce the frequency and severity of vertigo attacks, and secondarily to reduce hearing loss, tinnitus and aural fullness, thereby improving quality of life. The choice of treatment should always be conservative initially and tailored to the patient's main complaint.[12,16]

During the International Federation of Oto-Rhino-Laryngological Societies (IFOS) Congress in June 2017, a discussion among experts from various continents led to a minimal intercontinental consensus on the treatment of Ménière's disease.[12] This consensus is referenced in the German guideline on vestibular disorders, which was coauthored by Swiss clinical experts.[5] The recommended first-line treatments include diuretics (e.g. hydrochlorothiazide and acetazolamide) and betahistine, combined with lifestyle modifications (e.g. avoiding caffeine and adopting a low salt diet), vestibular rehabilitation and/or psychotherapy.[12] Note that the German guideline states that there are no clear recommendations for or against betahistine given the current evidence base.[5] After the first line of treatment, it is expected that 80% of the patients will experience remission of symptoms. For those who do not experience remission, the intratympanic injection of steroids (e.g. dexamethasone) is recommended as second-line treatment. The third-line treatment, determined by the patient's hearing function, could be either endolymphatic sac surgery (with a lower risk of hearing loss) or the intratympanic injection of gentamicin (with a higher risk of hearing loss). Destructive surgical treatments, including labyrinthectomy and vestibular neurectomy, are recommended as the fourth (and last) line of treatment.[12]

In the Swiss mediX guidelines, treatment of Ménière's disease is mentioned in relation to vertigo and tinnitus.[87,88] Medication indicated for the symptomatic treatment of vertigo in patients with Ménière's disease includes antihistamines (including dimenhydrinate and cinnarizine with dimenhydrinate), calcium channel blockers (cinnarizine and cinnarizine with dimenhydrinate) antiemetics and flunarizine. The Swiss guidelines explicitly state that there is no consensus among experts on the effectiveness of betahistine for the treatment of Ménière's disease.[87] The Swiss guidelines for the treatment of tinnitus mention that the evidence base for most tinnitus therapies is limited and that methodological quality of the available studies is very heterogenous. More specifically, the guidelines for the treatment of tinnitus in patients with Ménière's disease redirect to the guidelines for vertigo.[88]

9.1.2 Vertigo and tinnitus caused by other peripheral or central vestibular disorders

The Swiss guidelines for the treatment of tinnitus mention that the evidence base for most tinnitus therapies is limited and that methodological quality of the available studies is very heterogenous. The Swiss guidelines mention betahistine as a therapy without proven efficacy for tinnitus.[88] Multiple guidelines for the treatment of tinnitus, including European and German guidelines, advise against the routine use of medications, such as betahistine, anti-vertigo drugs (e.g. dimenhydrinate) and anticonvulsants, as they have not been proven to reduce symptoms and may cause negative side effects.[89–91] The medical treatment of vertigo should be targeted to the underlying cause. For example, for BPPV, dimenhydrinate or other anti-vertigo drugs may be considered for short-term management of symptoms such as nausea or vomiting, especially in patients experiencing severe symptoms after a repositioning procedure. Repositioning procedures (e.g. the Epley manoeuvre) are considered the primary treatment for BPPV.[5]

9.2 Existing HTA reports

Relevant HTA reports on betahistine or cinnarizine, with or without dimenhydrinate, for vertigo, tinnitus and hearing loss caused by Ménière's disease or for vertigo and tinnitus caused by other peripheral or central vestibular disorders were not found on the websites of the National Institute for Health and Care Excellence (NICE; the United Kingdom), the Institute for Clinical and Economic Review (ICER-US; the United States), Canada's Drug Agency (CDA), and the National Health Care Institute (ZIN; the Netherlands). On the website of NICE, an evidence review of betahistine for tinnitus was available. The identified evidence did not show a clinical difference between betahistine and placebo. No economic evaluations were identified.[92] Haute Autorité de Santé (HAS; France) concluded that Betaserc (24 mg) had moderate clinical benefit in the symptomatic treatment of Ménière's disease and vertigo of vestibular origin.[93] No evidence reports were identified for cinnarizine with or without dimenhydrinate on the website of HAS.

9.3 Ongoing RCTs on ClinicalTrials.gov and EU Clinical Trials Register

On 11 December 2023, a search was completed on ongoing RCTs. In ClinicalTrials.gov and EU Clinical Trials Register, 12 and 10 hits were screened, respectively. One ongoing RCT was found for the intervention betahistine prolonged release 48 mg/day compared with placebo in adult patients with Ménière's disease in Spain (***Table 61***). The estimated completion date of the RCT was not reported.

Since the number of pertinent RCTs on licensed betahistine use in patients with Ménière's disease is small, the sample sizes ranged from 10 to 147 (5 to 74 per study arm) and no effect of betahistine was shown, it is recommended to monitor the results of this ongoing RCT.

Table 61. Ongoing RCT fitting the eligibility criteria

Trial registry ID; country	Population; sample size	Intervention	Comparator	Outcomes	Trial status; estimated completion date	Funding
2020-005246-42[a]; Spain	Adult patients with Ménière's disease; n=340	Betahistine prolonged release 48 mg/day	– Betahistine conventional release 24 mg/day – Placebo	– Percentage significant responders[b] – Number of asymptomatic days (no vertigo attacks) – Change in number of monthly vertigo attacks – Hearing – Tinnitus – Dizziness Handicap Inventory	Ongoing; not reported	Intas Pharmaceuticals Ltd., India

Notes
a = EudraCT Number.
b = Defined by 1-point change in any 2 of intensity, duration and frequency of vertigo attacks score based on GISFaV self-rating scale against baseline score.

9.4 Off-label betahistine use for Ménière's disease

Two included RCTs reported data on off-label betahistine use for Ménière's disease.[32,36] The study characteristics and results tables are enclosed in ***Appendix E.***

Adrion et al 2016 studied the efficacy and safety of 9 months low-dose betahistine treatment of 48 mg/day (n=73, mean age 56.1±11.1 years, 53% male), high-dose betahistine of 144 mg/day (n=74, mean age 56.1±12.6 years, 47% male), and placebo (n=74, mean age 54.5±12.8 years, 47% male) in patients with Ménière's disease in Germany.[39] The results for high-dose betahistine versus placebo were in line with the results for low-dose betahistine versus placebo. No statistically significant differences were found for high-dose betahistine compared to placebo in vertigo attack frequency (RR 1.01 [95% CI 0.92 to 1.11]), tinnitus intensity (aMD -3.34 dB [95% CI -9.74 to 3.06]), and hearing loss (range aMD from -0.68 dB [95% CI -4.75 to 3.39] at 2000 Hz to +1.15 dB [95% CI -3.27 to 5.56] at 1000 Hz). Also no statistically significant differences were reported for disease-specific HRQoL assessed with the dizziness handicap inventory (aMD -0.03 [95% CI -0.27 to 0.22]; mean total score range 0 [best]–4 [worst]), vestibular disorders activities of daily living questionnaire (aMD -0.06 [95% CI -0.33 to 0.20]; score range 1 [best]–10 [worst]), and mini-tinnitus impairment questionnaire (aMD -0.016 [95% CI -0.15 to 0.11]; score range 0 [best]–24 [worst]). No statistically significant difference was found in the occurrence of serious adverse events for high-dose betahistine versus placebo (RR 1.27 [95% CI 0.62 to 2.62]).

During a study of 24 months in Romania and Italy, Albu et al 2016 assessed the efficacy and safety of intratympanic dexamethasone (ITD) treatment combined with high-dose betahistine of 144 mg/day (n=33, mean age not reported, 45% male) compared to ITD plus placebo (n=33, mean age not reported, 36% male) in adult patients with Ménière's disease, diagnosed according to the AAO-HNS 1995 criteria.[43] Comorbidities or other comedication were not reported in the article. A statistically significant larger percentage of patients treated with ITD plus high-dose betahistine versus ITD plus placebo attained complete vertigo control (73% versus 44%; RR 1.68 [95% CI 1.07 to 2.62]) or substantial vertigo control (90% versus 66%; RR 1.37 [95% CI 1.04 to 1.81]). Disease-

specific HRQoL assessed with the functional level score (FLS) was also statistically significant better in the ITD plus high-dose betahistine group; level 1 FLS was reached in 22 (73%) patients and level 2 in 7 (23%) patients versus respectively 15 (47%) patients and 8 (25%) patients in the ITD plus placebo group. No statistically significant differences in tinnitus severity and hearing levels were found between the treatment arms. No serious adverse events were encountered in patients treated with ITD plus high-dose betahistine, but no data on adverse events was reported for the ITD plus placebo arm.

10. Discussion

A rigorous systematic review methodology, adhering to international methodological standards, was applied to identify, critically appraise, analyse and summarise pertinent evidence on the predefined outcomes of interest in order to minimise bias. Two systematic literature searches were conducted for the clinical systematic review to search RCTs on betahistine and cinnarizine with or without dimenhydrinate for vertigo, tinnitus and hearing loss caused by Ménière's disease or for vertigo and tinnitus caused by other peripheral or central vestibular disorders. Based on the medication and population the data was stratified in 4 groups. The evidence base on licensed use of betahistine or cinnarizine with or without dimenhydrinate was limited, with 1 to 4 RCTs included for the groups, and relatively small sample sizes. No publication date limit was applied in the systematic literature search. A common limitation of older studies compared to more recent studies is poor reporting of the methodology and results and lack of using validated outcome measures. When a study did not clearly state that the allocation of participants was randomised, the study was excluded during full-text selection as non-RCT. RCTs with relevant data missing for valid data interpretation were included in the clinical systematic review, but these results were not included in the data synthesis and instead enclosed in an appendix. The RCTs hardly reported data on clinical relevance of treatment effects. The findings of the systematic reviews were broadly similar to evidence described in NICE's evidence report and earlier Cochrane reports.[92,94–96] Differences were likely to originate from differences in inclusion and exclusion criteria.

Multiple factors might affect the treatment effect, such as underlying cause of vertigo or tinnitus, concomitant diseases, differences in drug dose and duration, prior or concomitant medication use, and missing data. Part of these data was scarcely or not reported in the included RCTs. Populations included in the studies did not cover the full spectrum of the indications that fall within the scope of the licensed indications. Furthermore, criteria to diagnose a disease can change over time. The diagnosis of definite Ménière's disease was uniform and based on the AAO-HNS 1995 criteria in 3 RCTs and 1 RCT did not report information on the definition of Ménière's disease. However, no details were reported on concomitant diseases. Clear definitions for vertigo and tinnitus were lacking. The vertigo populations in the included RCTs were very heterogeneous, with different diseases or specific symptoms applied in the inclusion and exclusion criteria. Pytel et al 2007 highlighted that patients with vestibular vertigo of central, peripheral or central/peripheral origin were included in their study to mirror the "typical" vertigo patient for whom cinnarizine with dimenhydrinate is prescribed by general practitioners, otologists and neurologists.[38] Furthermore, the complexity of the disease and lack of validated instruments complicates measuring the subjective outcome vertigo.[32,41] The occurrence of concomitant diseases in patients with vertigo was reported only in 2 RCTs, but not specified in detail. For instance, a large proportion of patients with Ménière's disease also suffers from vestibular migraine.[97] This might affect the conclusions on the effectiveness of treatments for Ménière's disease in clinical studies. Betahistin might have different effects on Ménière's disease and vestibular migraine, because of differences in underlying pathology of the

diseases. As such, not excluding patients with vestibular migraine in clinical studies introduces an important bias. However, even when vestibular migraine is applied as exclusion criterion, participants might still report a history of migraine headaches, for example in the RCT of Adrion et al 2016.[39] In addition, differences in dosage and treatment duration might affected the study results. The dosage of betahistine ranged from 24 mg/day to 48 mg/day (i.e. in line with licensed betahistine use), though the treatment duration varied between 1 and 10 months. The 2 included RCTs on cinnarizine with dimenhydrinate in patients with vertigo studied the same dosage and treatment duration. Five RCTs applied a wash-out period before the start of the study. Details on prior or concomitant medication use were not reported in the included RCTs. As highlighted in the quality assessment section, missing data was a frequent issue in the included studies.

The clinical course of Ménière's disease is unpredictable and cyclical.[32,68] This potentially complicates the assessment of efficacy in this disease, when spontaneous improvements in either the treatment or placebo arm are interpreted as genuine treatment effects. Likewise, spontaneous deterioration in the treatment or placebo arm could be interpreted as lack of efficacy/placebo effect. When sample sizes are large enough such natural variation would be balanced.

No cost-effectiveness studies were found in the economic systematic review, despite the long history of betahistine and cinnarizine for the treatment of Ménière's disease, vertigo and tinnitus. Due to a lack of evidence for a positive treatment effect in the clinical review, no *de-novo* cost-effectiveness models were built for betahistine or cinnarizine without dimenhydrinate for the treatment of Ménière's disease, vertigo or tinnitus, nor for cinnarizine with dimenhydrinate for treatment of Ménière's disease. Likewise, the evidence base to inform the cost-effectiveness model for cinnarizine with dimenhydrinate for the treatment of vertigo caused by other disorders than Ménière's disease was very small, both with respect to model structure as well as parameter input. In concordance with the model by Stratmann et al 2006, the model structure was based on treatment response.[50] As patient level data was unavailable, treatment response was required to be aligned to the evidence from the literature (i.e. the model used a 50% reduction in MVS, as measured in Pytel et al 2007, as response criterion). Alternative response criteria could not be explored with the available evidence. Informing model parameter was also challenging due to the limited amount of evidence. No information was available on utility values. The lack of utility values prevented conducting a cost-utility analysis and a cost-effectiveness analysis was conducted instead. Although this still provides valuable information, the comparability of the results to interventions for other diseases is strongly diminished by not taking a cost-utility approach. The absence of a MCID for a reduction in MVS, complicates the interpretation of the cost-effectiveness outcomes. However, since cinnarizine with dimenhydrinate is dominant compared to no treatment in most analyses, this issue does not appear to be of a significant concern for the current analyses. In addition, information on healthcare consumption was limited too. Only one study (Stratmann et al 2006) reported on the additional healthcare usage for non-responders.[50] Expert opinion was necessary to inform the activities that relate to such a consultation. Several scenario analyses were conducted to assess the

impact of the assumptions on healthcare utilisation. These scenario analyses showed the robustness of the results with respect to these assumptions. It should be noted that the cost-effectiveness model was built for vertigo caused by other disorders than Ménière's disease. Given the lack of evidence for a positive treatment effect of cinnarizine with dimenhydrinate for the treatment of Ménière's disease, the results of the cost-effectiveness analyses should not be used to inform reimbursed decisions on cinnarizine with dimenhydrinate for the treatment of Ménière's disease.

Cinnarizine with dimenhydrinate is licensed for treatment of vertigo without specification of the underlying cause in Switzerland. The data used for the BI calculations for cinnarizine with dimenhydrinate were derived from SASIS. These data could not be differentiated according to indication. For the BI calculations, expert opinion was necessary on the proportion of patients using cinnarizine with dimenhydrinate for the treatment of vertigo caused by Ménière's disease and the proportion of patients using cinnarizine with dimenhydrinate for the treatment of vertigo caused by other disorders than Ménière's disease. As cinnarizine with dimenhydrinate was assumed to have different effects in the two populations (leading to different effects on healthcare consumption in the two populations), this proportion was influential in establishing the total budget impact. A scenario analysis was run to show the impact of this parameter on the budget impact estimate, showing that alternative values could result in a positive budget impact rather than budget savings shown in the base case analysis.

11. Conclusions

The evidence base was limited. The clinical evidence in adult patients with Ménière's disease suggests little or no difference in the treatment effect of betahistine compared with placebo on vertigo attack frequency (1 RCT; moderate certainty evidence), tinnitus intensity (1 RCT; low certainty evidence), hearing loss (1 RCT; low certainty evidence), and disease-specific HRQoL (1 RCT; moderate certainty evidence). Betahistine may improve disease-specific HRQoL compared with no treatment in patients with Ménière's disease, but the evidence is very uncertain (1 RCT; very low certainty evidence). Betahistine may be well tolerated in patients with Ménière's disease, with little or no difference in the occurrence of serious adverse events compared to placebo (2 RCTs; low certainty evidence). In adult patients with diverse vertigo aetiologies the evidence on the effect of betahistine on vertigo compared with placebo is lacking, seems not consistent and is very uncertain (3 RCTs; very low certainty evidence). Betahistine may be well tolerated in patients with vertigo, with no serious adverse events encountered with betahistine or placebo treatment, but the evidence is very uncertain (3 RCTs; very low certainty evidence). In adult patients with idiopathic subjective tinnitus cinnarizine may show little or no difference in tinnitus symptoms compared with placebo, but the evidence is very uncertain (1 RCT; very low certainty evidence). No data was reported on serious adverse events. In adult patients with diverse vertigo aetiologies cinnarizine with dimenhydrinate treatment probably results in an improvement of vertigo symptoms compared to placebo (2 RCTs; moderate certainty evidence). Cinnarizine with dimenhydrinate may be well tolerated in patients with vertigo, with no serious adverse events encountered with cinnarizine with dimenhydrinate or placebo treatment (2 RCTs; low certainty evidence).

From a health economic perspective, cinnarizine with dimenhydrinate dominated no treatment (i.e. more effective at lower costs) in the treatment of vertigo caused by other disorders than Ménière's disease. The use of cinnarizine with dimenhydrinate for the treatment of Ménière's disease and the treatment of vertigo caused by other disorders than Ménière's disease was associated with projected budget savings of CHF 1.2 million over a 5-year period. Note that the extent to which these savings can be expected depends on the accuracy of the estimated distribution between patients using cinnarizine with dimenhydrinate for vertigo caused by Ménière's disease and patients using it for vertigo caused by other disorders. The cost-effectiveness of betahistine and cinnarizine without dimenhydrinate was not assessed, because no evidence for a positive treatment effect was shown in the clinical review. Despite the lack of evidence for a positive treatment effect of betahistine and cinnarizine, these treatments are currently reimbursed in Switzerland, and hence associated with a budgetary impact. Budget impact analyses estimated that total costs of betahistine were CHF 17.2 million over a 5-year period. Over a 5-year period, total projected costs of cinnarizine were CHF 0.8 million. Finally, the treatment of Ménière's disease, vertigo and tinnitus was associated with several ethical, social and organisational issues.

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13. Appendices

A. Search strategy clinical systematic literature search

Table 62. PubMed (MEDLINE), primary systematic literature search

Population	"Meniere Disease"[Mesh] OR meniere*[tiab] OR "Vertigo"[Mesh] OR vertigo*[tiab] OR "Tinnitus"[Mesh] OR tinnitus[tiab]
Intervention	"Betahistine"[Mesh] OR "Cinnarizine"[Mesh] OR acuver*[tiab] OR am-125[tiab] OR am-201[tiab] OR am125[tiab] OR am201[tiab] OR antivom*[tiab] OR behistep*[tiab] OR bestin*[tiab] OR betabare*[tiab] OR betabire*[tiab] OR betagen*[tiab] OR betahecon*[tiab] OR betahistin*[tiab] OR beta-histin*[tiab] OR betalune*[tiab] OR betaserc*[tiab] OR betaserk*[tiab] OR fortamid*[tiab] OR histigen*[tiab] OR lectil[tiab] OR marac[tiab] OR marak[tiab] OR meniserc*[tiab] OR microser*[tiab] OR neatin*[tiab] OR pt-9[tiab] OR serc[tiab] OR sinmenier*[tiab] OR vasomotal*[tiab] OR vertiserc*[tiab] OR aplactan*[tiab] OR aplexal*[tiab] OR apomitere*[tiab] OR apotomin*[tiab] OR artate*[tiab] OR carecin*[tiab] OR cerebolan*[tiab] OR cerepar*[tiab] OR cibine*[tiab] OR cimarizine*[tiab] OR cinabioquim*[tiab] OR cinaperazine*[tiab] OR cinazyn*[tiab] OR cinnabene*[tiab] OR cinnacet*[tiab] OR cinnaforte*[tiab] OR cinnageron*[tiab] OR cinnarazin*[tiab] OR cinnarizin*[tiab] OR cinarizin*[tiab] OR cinnipirine*[tiab] OR cinniprine*[tiab] OR corathiem*[tiab] OR denapol*[tiab] OR dimitron*[tiab] OR dimitronal*[tiab] OR eglen*[tiab] OR giganten*[tiab] OR glanil*[tiab] OR hilactan*[tiab] OR ixertol*[tiab] OR katoseran*[tiab] OR labyrin[tiab] OR lazeta*[tiab] OR marisan*[tiab] OR md-516*[tiab] OR 516-md[tiab] OR midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r516[tiab] OR roin[tiab] OR sedatromin*[tiab] OR sepan*[tiab] OR siptazin*[tiab] OR spaderizine*[tiab] OR stugeron*[tiab] OR stutgeron*[tiab] OR stutgin*[tiab] OR arlevert*[tiab]
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints: NOT (congress[pt] OR preprint[pt])
Search date	9 November 2023

Table 63. Embase.com, primary systematic literature search

Population	'Meniere disease'/exp OR meniere*:ti,ab OR 'vertigo'/exp OR vertigo*:ti,ab OR 'tinnitus'/exp OR tinnitus:ti,ab
Intervention	'betahistine'/exp OR 'cinnarizine'/exp OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516-md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r516:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints/select other publication types: AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
Search date	9 November 2023

Table 64. Cochrane Library, primary systematic literature search

Population	[mh "Meniere Disease"] OR meniere*:ti,ab OR [mh Vertigo] OR vertigo*:ti,ab OR [mh Tinnitus] OR tinnitus:ti,ab
Intervention	[mh Betahistine] OR [mh Cinnarizine] OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r516:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints: NOT (congress:pt OR preprint:pt)
Search date	9 November 2023

Table 65. ClinicalTrials.gov and EU Clinical Trials Register

Population	meniere OR vertigo OR tinnitus
Intervention	betahistine OR cinnarizine
Comparator	No search string
Outcome	No search string
Search date	11 December 2023

Table 66. PubMed (MEDLINE), additional systematic literature search

Betahistine and specific conditions	(vestibular migraine[tiab] OR "Vertebrobasilar Insufficiency"[Mesh] OR vertebrobasilar insufficienc*[tiab] OR vertebro-basilar insufficienc*[tiab] OR vertebrobasilar ischemia[tiab] OR vertebro-basilar ischemia[tiab] OR "Ischemic Attack, Transient"[Mesh] OR transient ischemic attack*[tiab] OR TIA[tiab] OR TIAs[tiab] OR (anterior inferior cerebellar artery[tiab] AND infarct*[tiab]) OR (anterior inferior cerebellar artery[tiab] AND stroke[tiab]) OR (labyrinthine artery[tiab] AND infarct*[tiab]) OR (labyrinthine artery[tiab] AND stroke[tiab])) AND ("Betahistine"[Mesh] OR acuver*[tiab] OR am-125[tiab] OR am-201[tiab] OR am125[tiab] OR am201[tiab] OR antivom*[tiab] OR behistep*[tiab] OR bestin*[tiab] OR betabare*[tiab] OR betabire*[tiab] OR betagen*[tiab] OR betahecon*[tiab] OR betahistin*[tiab] OR beta-histin*[tiab] OR betalune*[tiab] OR betaserc*[tiab] OR betaserk*[tiab] OR fortamid*[tiab] OR histigen*[tiab] OR lectil[tiab] OR marac[tiab] OR marak[tiab] OR meniserc*[tiab] OR microser*[tiab] OR neatin*[tiab] OR pt-9[tiab] OR serc[tiab] OR sinmenier*[tiab] OR vasomotal*[tiab] OR vertiserc*[tiab])
Cinnarizine with or without dimenhydrinate and specific conditions	(vestibular migraine[tiab] OR "Benign Paroxysmal Positional Vertigo"[Mesh] OR BPPV[tiab] OR "Vertebrobasilar Insufficiency"[Mesh] OR vertebrobasilar insufficienc*[tiab] OR vertebro-basilar insufficienc*[tiab] OR vertebrobasilar ischemia[tiab] OR vertebro-basilar ischemia[tiab] OR "Ischemic Attack, Transient"[Mesh] OR transient ischemic attack*[tiab] OR TIA[tiab] OR TIAs[tiab] OR (anterior inferior cerebellar artery[tiab] AND infarct*[tiab]) OR (anterior inferior cerebellar artery[tiab] AND stroke[tiab]) OR (labyrinthine artery[tiab] AND infarct*[tiab]) OR (labyrinthine artery[tiab] AND stroke[tiab])) AND ("Cinnarizine"[Mesh] OR aplactan*[tiab] OR aplexal*[tiab] OR apomitere*[tiab] OR apotomin*[tiab] OR artate*[tiab] OR carecin*[tiab] OR cerebolan*[tiab] OR cerepar*[tiab] OR cibine*[tiab] OR cimarizine*[tiab] OR cinabioquim*[tiab] OR cinaperazine*[tiab] OR cinazyn*[tiab] OR cinnabene*[tiab] OR cinnacet*[tiab] OR cinnaforte*[tiab] OR cinnageron*[tiab] OR cinnarazin*[tiab] OR cinnarizin*[tiab] OR cinarizin*[tiab] OR cinnipirine*[tiab] OR cinniprine*[tiab] OR corathiem*[tiab] OR denapol*[tiab] OR dimitron*[tiab] OR dimitronal*[tiab] OR eglen*[tiab] OR giganten*[tiab] OR glanil*[tiab] OR hilactan*[tiab] OR ixertol*[tiab] OR katoseran*[tiab] OR labyrin[tiab] OR lazeta*[tiab] OR marisan*[tiab] OR md-516*[tiab] OR 516-md[tiab] OR midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r516[tiab] OR roin[tiab] OR sedatromin*[tiab] OR sepan*[tiab] OR siptazin*[tiab] OR spaderizine*[tiab] OR stugeron*[tiab] OR stutgeron*[tiab] OR stutgin*[tiab] OR arlevert*[tiab])
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints: NOT (congress[pt] OR preprint[pt])
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

Table 67. Embase.com, additional systematic literature search

Betahistine and specific conditions	('vestibular migraine':ti,ab OR 'vertebrobasilar insufficiency'/exp OR 'vertebrobasilar insufficienc*':ti,ab OR 'vertebro-basilar insufficienc*':ti,ab OR 'vertebrobasilar ischemia':ti,ab OR 'vertebro-basilar ischemia':ti,ab OR 'transient ischemic attack'/exp OR 'transient ischemic attack*':ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ('anterior inferior cerebellar artery':ti,ab AND infarct*:ti,ab) OR ('anterior inferior cerebellar artery':ti,ab AND stroke:ti,ab) OR ('labyrinthine artery':ti,ab AND infarct*:ti,ab) OR ('labyrinthine artery':ti,ab AND stroke:ti,ab)) AND ('betahistine'/exp OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab)
Cinnarizine with or without dimenhydrinate and specific conditions	('vestibular migraine':ti,ab OR 'benign paroxysmal positional vertigo'/exp OR BPPV:ti,ab OR 'vertebrobasilar insufficiency'/exp OR 'vertebrobasilar insufficienc*':ti,ab OR 'vertebro-basilar insufficienc*':ti,ab OR 'vertebrobasilar ischemia':ti,ab OR 'vertebro-basilar ischemia':ti,ab OR 'transient ischemic attack'/exp OR 'transient ischemic attack*':ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ('anterior inferior cerebellar artery':ti,ab AND infarct*:ti,ab) OR ('anterior inferior cerebellar artery':ti,ab AND stroke:ti,ab) OR ('labyrinthine artery':ti,ab AND infarct*:ti,ab) OR ('labyrinthine artery':ti,ab AND stroke:ti,ab)) AND ('cinnarizine'/exp OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516-md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r51:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab)
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints/select other publication types: AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

Table 68. Cochrane Library, additional systematic literature search

Betahistine and specific conditions	("vestibular migraine":ti,ab OR [mh "Vertebrobasilar Insufficiency"] OR (vertebrobasilar NEXT insufficienc*):ti,ab OR (vertebro-basilar NEXT insufficienc*):ti,ab OR (vertebrobasilar NEXT ischemia):ti,ab OR (vertebro-basilar NEXT ischemia):ti,ab OR [mh "Ischemic Attack, Transient"] OR ("transient ischemic" NEXT attack*):ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ("anterior inferior cerebellar artery":ti,ab AND infarct*:ti,ab) OR ("anterior inferior cerebellar artery":ti,ab AND stroke:ti,ab) OR ("labyrinthine artery":ti,ab AND infarct*:ti,ab) OR ("labyrinthine artery":ti,ab AND stroke:ti,ab)) AND ([mh Betahistine] OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab)
Cinnarizine with or without dimenhydrinate and specific conditions	("vestibular migraine":ti,ab OR [mh "Benign Paroxysmal Positional Vertigo"] OR BPPV:ti,ab OR [mh " Vertebrobasilar Insufficiency"] OR (vertebrobasilar NEXT insufficienc*):ti,ab OR (vertebro-basilar NEXT insufficienc*):ti,ab OR (vertebrobasilar NEXT ischemia):ti,ab OR (vertebro-basilar NEXT ischemia):ti,ab OR [mh "Ischemic Attack, Transient"] OR ("transient ischemic" NEXT attack*):ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ("anterior inferior cerebellar artery":ti,ab AND infarct*:ti,ab) OR ("anterior inferior cerebellar artery":ti,ab AND stroke:ti,ab) OR ("labyrinthine artery":ti,ab AND infarct*:ti,ab) OR ("labyrinthine artery":ti,ab AND stroke:ti,ab)) AND ([mh Cinnarizine] OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r51:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab)
Comparator	No search string
Outcome	No search string
Limits	No conference abstracts and preprints: NOT (congress:pt OR preprint:pt)
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

B. Excludes during full-text selection clinical systematic review

Table 69. Excluded studies found with the clinical systematic literature search for RCTs

Reference	Reason for exclusion
No author. Betahistine hydrochloride (serc) for Ménière's syndrome. The Medical letter on drugs and therapeutics. 1967;9(8):29-30.	Narrative review
No author. An agent for the amelioration of vertigo in Ménière's syndrome. Betahistine hydrochloride (Serc). JAMA : the journal of the American Medical Association. 1968;203(13):1122.	Irrelevant publication type (statement)
No author. Drug treatment of vertigo and Ménière's disease: Cinnarizine and betahistine. Drug and Therapeutics Bulletin. 1981;19(5):17-8.	Narrative review
No author. Supportive therapy with dimenhydrinate in combination with cinnarizine in vertigo. Therapiewoche. 1996;46(3):175.	Comparator out of scope (no 'placebo or no treatment' as control group)
No author. Therapy of vertigo with cinnarizine and dimenhydrinate: Combination treatment is more effective. Therapie und Erfolg Neurologie Psychiatrie. 1997;11(12):927-8.	Narrative review
No author. Controversial betahistine: Efficacy in acute vertigo and Ménière's disease at placebo level? Deutsche Apotheker Zeitung. 2016;156(44):42.	Narrative review
Acar B, Karasen RM, Buran Y. Efficacy of medical therapy in the prevention of residual dizziness after successful repositioning maneuvers for Benign Paroxysmal Positional Vertigo (BPPV). B-ENT. 2015;11(2):117-21.	Population out of scope (patients with BPPV treated with betahistine)
Ahmadzai N, Cheng W, Kilty S, Esmaeilisaraji L, Wolfe D, Bonaparte J, et al. Pharmacologic and surgical therapies for patients with Ménière's disease: A systematic review and network meta-analysis. PLoS ONE. 2020;15(9).	Systematic review
Albernaz PL, Ganança MM, Menon AD. The treatment of equilibrium and hearing problems using Cinnarizine (R-516). Hospital. 1968;74(3):787-91.	Language out of scope (article in Portuguese)
Ali M, Tanveer, Awan AS, Khan A, Zaki A, Mudassir M. Epley's Maneuver Alone Vs. Epley's Maneuver with Betahistine for Mild"Paroxysmal Positional Vertigo" A Tertiary Care Hospital Study. Pakistan Journal of Medical and Health Sciences. 2022;16(12):313-4.	Population out of scope (patients with BPPV treated with betahistine)
Basta D, Borsellino L, Ernst A. Antivertiginous drug therapy does not hinder the efficacy of individualized vibrotactile neurofeedback training for vestibular rehabilitation - a randomized trial. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation. 2017;40(4):333-8.	No stratified data reported for patients with vertigo
Bertrand, RA. Modification of the vestibular function with betahistine HCl. The Laryngoscope. 1971;81(6):889-98.	No RCT
Bertrand, RA. Méniére's disease: subjective and objective evaluation of medical treatment with betahistine HCl. Acta oto-laryngologica Supplementum. 1972;305:48-69.	No RCT
Burkin A. Betahistine treatment for Ménière's Syndrome. Clinical medicine. 1967;74:41-8.	Outcome out of scope
Byun YJ, Levy DA, Nguyen SA, Brennan E, Rizk HG. Treatment of Vestibular Migraine: A Systematic Review and Meta-analysis. Laryngoscope. 2021;131(1):186-94.	Systematic review
Castagno LA. Tinnitus: A therapeutic trial with cinnarisine, primidone and placebo. Folha Medica. 1989;99(5):279-84.	Language out of scope (article in Portuguese)
Castellini V. Clinical and electronystagmographic experience with a new drug containing cinnarizine in the treatment of vertigo. Bollettino delle malattie dell'orecchio, della gola, del naso. 1969;87(2):107-31.	Intervention out of scope (cinnarizine given as combination drugs with Auricovit S)
Castilho GL, Dias NH, Martins RHG. A triple blind, placebo controlled, randomised controlled trial of betahistine dihydrochloride in the treatment of primary tinnitus. Clinical Otolaryngology. 2023;48(1):50-7.	Population out of scope (patients with tinnitus excluding those with Ménière's disease and vestibular symptoms treated with betahistine)
Cekkayan S, Ozlüoğlu L, Yoloğlu S, Söylemezoğlu S, Erpek G. Comparison of the efficiency of betahistine hydrochloride and gingko biloba extract in tinnitus patients. KBB ve baş boyun cerrahisi dergisi. 1996;4:19-22.	Language out of scope (article in Turkish)

Chen JJ, Chen YW, Zeng BY, Hung CM, Zeng BS, Stubbs B, et al. Efficacy of pharmacologic treatment in tinnitus patients without specific or treatable origin: A network meta-analysis of randomised controlled trials. EClinicalMedicine. 2021;39:101080.	Systematic review
Claes J, Van De Heyning PH. Medical treatment of Ménière's disease: A review of literature. Acta Oto-Laryngologica, Supplement. 1997(526):37-42.	Systematic review
Claes J, Van de Heyning PH. A review of medical treatment for Ménière's disease. Acta Oto-Laryngologica, Supplement. 2000(544):34-9.	Systematic review
Della Pepa C, Guidetti G, Eandi M. Betahistine in the treatment of vertiginous syndromes: a meta-analysis. Acta otorhinolaryngologica Italica : organo ufficiale della Società italiana di otorinolaringologia e chirurgia cervico-facciale. 2006;26(4):208-15.	Systematic review
Devantier L, Hougaard D, Händel MN, Liviu-Adelin Guldfred F, Schmidt JH, Djurhuus B, et al. Using betahistine in the treatment of patients with Menière's disease: a meta-analysis with the current randomized-controlled evidence. Acta Oto-Laryngologica. 2020;140(10):845-53.	Systematic review
Dobie RA. A review of randomized clinical trials in tinnitus. Laryngoscope. 1999;109(8):1202-11.	Systematic review
Elia JC. Double-blind evaluation of a new treatment for Ménière's syndrome. JAMA. 1966;196(2):187-9.	Cross-over trial without data before cross-over
Euctr DE. Medical treatment of Menière s disease with betahistine: a placebo-controlled, dose-finding study. EUCTR [wwwclinicaltrialsregistereu]. 2005.	Irrelevant publication type (trial registry)
Fischer A, Van Elferen LWM. Betahistine in the treatment of paroxysmal attacks of vertigo. A double blind investigation. TGO - tijdschrift voor therapie geneesmiddel en onderzoek. 1985;10(9):933-7.	Language out of scope (article in Dutch)
Frew IJ, Menon GN. Betahistine hydrochloride in Méniére's disease. Postgraduate medical journal. 1976;52(610):501-3.	Cross-over trial without data before cross-over
Ganança Maurício M, Caovilla Heloisa H. Double-blind method, randomized with the use of 3 cinarizine schedule in the treatment of vertigo. Revista brasileira de medicina. 1990;47(10):524-8.	Language out of scope (article in Portuguese)
Greiner GF, Conraux C, Collard M, Gentine A, Feblot P, Gillet B. [Treatment of Ménière's vertigo with betahistine]. Rev Otoneuroophtalmol. 1975;47(3):227-36.	No RCT
Guneri EA, Kustutan O. The effects of betahistine in addition to epley maneuver in posterior canal benign paroxysmal positional vertigo. Otolaryngology - Head and Neck Surgery. 2012;146(1):104-8.	Population out of scope (patients with BPPV treated with betahistine)
Hausler R, Sabani E, Rohr M. Effect of cinnarizine on various types of vertigo. Clinical and electronystagmographic results of a double-blind study. Acta Oto-Rhino-Laryngologica Belgica. 1989;43(2):177-84.	No RCT (allocation not randomised)
Hicks JJ, Hicks JN, Cooley HN. Ménière's disease. Archives of otolaryngology (Chicago, Ill : 1960). 1967;86(6):610-3.	No RCT
Hommes OR. A study of the efficacy of betahistine in Méniére's syndrome. Acta oto-laryngologica Supplementum. 1972;305:70-9.	No RCT
Hong J, Bi Y, Fang L. Research of association of modified Epley maneuver and betahistine for treating posterior semicircular canal benign paroxysmal positional vertigo. Chin General Pract. 2012;15:622-4.	Language out of scope (article in Chinese)
İnan HC, Kıraç M. An Evaluation of the Effects of Betahistine and Dimenhydrinate on Posterior Canal Benign Paroxysmal Positional Vertigo. Turk Arch Otorhinolaryngol. 2019;57(4):191-6.	Population out of scope (patients with BPPV treated with betahistine)
Jakobs P, Martin G. The therapy of tinnitus resulting from blast injury. HNO. 1978;26(3):104-6.	Population out of scope (patients with tinnitus due to blast injury treated with betahistine)
Jalali MM, Gerami H, Saberi A, Razaghi S. The Impact of Betahistine versus Dimenhydrinate in the Resolution of Residual Dizziness in Patients with Benign Paroxysmal Positional Vertigo: A Randomized Clinical Trial. Annals of Otology, Rhinology and Laryngology. 2020;129(5):434-40.	Population out of scope (patients with BPPV treated with betahistine)
James A, Burton MJ. Betahistine for Ménière's disease or syndrome. Cochrane Database of Systematic Reviews. 2001(1).	Duplicate article

James AL, Burton MJ. Betahistine for Menière's disease or syndrome. Cochrane database of systematic reviews (Online). 2001(1):CD001873.	Systematic review
James AL, Thorp MA. Menière's disease. BMJ clinical evidence. 2007;2007.	Systematic review
James A, Burton MJ. Betahistine for Ménière's disease or syndrome. Cochrane Database of Systematic Reviews. 2020;2001(1).	Systematic review
Kaur J, Shamanna K. Management of benign paroxysmal positional vertigo: A comparative study between epleys Manouvre and Betahistine. International Tinnitus Journal. 2017;21(1):30-4.	Population out of scope (patients with BPPV treated with betahistine)
Kay NJ. Oral chemotherapy in tinnitus. British Journal of Audiology. 1981;15(2):123-4.	Inadequate data (incomplete data)
Khan BH, Ahmed Z, Khan RA. Effects of diuretics and vasodilators therapy in Ménière's disease. Biomedica. 2011;27(2):114-8.	Comparator out of scope (vitamin as control group)
Kingma H, Bonink M, Meulenbroeks A, Konijnenberg H. Dose dependent effect of Betahistine of the vestibulo-ocular reflex: a double blind placebo controlled study in patients with paroxismal vertigo. Anales de otorrinolaringología mexicana. 1997;42(4):173-9. *Published in English in:* Kingma H, Bonink M, Meulenbroeks A, Konijnenberg H. Dose-dependent effect of betahistine on the vestibulo-ocular reflex: a double-blind, placebo controlled study in patients with paroxysmal vertigo. Acta Otolaryngol. 1997 Sep;117(5):641-6.	Outcome out of scope
Kirtane MV, Bhandari A, Narang P, Santani R. Cinnarizine: A Contemporary Review. Indian J Otolaryngol Head Neck Surg. 2019;71:1060-8.	Systematic review
Legent F, Calais C, Cellier D. Trial of betahistine in paroxysmal vertigo. Concours medical. 1988;110:2539-43.	No RCT (allocation not randomised)
Li Y, Cui L, Dong W. The clinical effects of betahistine mesilate tablets combined with manual reduction in treatment of benign paroxysmal positional vertigo. Hebei Med J. 2021;43:1350-3.	Language out of scope (article in Chinese)
Li W, Sun J, Zhao Z, Xu J, Wang H, Ding R, et al. Efficacy of Epley's maneuver plus betahistine in the management of PC-BPPV: A systematic review and meta-analysis. Medicine (United States). 2023;102(13):E33421.	Systematic review
Maqbool S, Ahmed B, Manzoor T. Eifficacy of betahistine hydrocholride in tinnitus due to noise-induced hearing loss. Pakistan armed forces medical journal. 2010;60(1).	Population out of scope (patients with tinnitus due to noise-induced hearing loss treated with betahistine)
Mashali L, Rahimi S, Rekabi H, Rahimi P. The comparative study of two drugs of carbamazepine and betahistine on tinnitus improvement. International Journal of Pharmacy and Technology. 2016;8(3):14774-81.	Population out of scope (patients with tinnitus excluding those with Ménière's disease treated with betahistine)
Meyer ED. Treatment of Ménière disease with betahistine dimesilate (Aequamen)--double-blind study versus placebo (crossover). Laryngologie, Rhinologie, Otologie. 1985;64(5):269-72.	Cross-over trial without data before cross-over
Muhammad T, Ahmed E, Habib M, Rasheed MT, Arshad M, Samin KA. Comparison of Effectiveness of Epley s Maneuver only and Epley s Maneuver plus Betahistinein the Management of Benign Paroxysmal Positional Vertigo. Pakistan Journal of Medical and Health Sciences. 2021;15(4):1254-6.	Population out of scope (patients with BPPV treated with betahistine)
Murdin L, Hussain K, Schilder AG. Betahistine for symptoms of vertigo. Cochrane Database Syst Rev. 2016;2016(6):Cd010696.	Systematic review
NICE Evidence Reviews Collection. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2020.; 2020 2020.	Systematic review
Nauta JJ. Meta-analysis of clinical studies with betahistine in Ménière's disease and vestibular vertigo. Eur Arch Otorhinolaryngol. 2014;271(5):887-97.	Systematic review
Nietsch P. Forms of vestibular vertigo. Evaluation of a clinical trial (phase IV) of Ribrain in 3550 patients. Die Medizinische Welt. 1983;34(25):736-7.	No RCT
Okamoto K, Hazeyama F, Taira T, Yoshida A, Onoda T. Therapeutic results of betahistine on Ménière's disease. Multi-variable analysis of the results of the double blind test and Fisher's evaluation method. Iryo. 1968;22(5):650-66.	Language out of scope (article in Japanese)

Oosterveld WJ. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. Journal of Laryngology and Otology. 1984;98(1):37-41.	No RCT (allocation not randomised)
Philipszoon AJ. Influence of cinnarizine on the labyrinth and on vertigo. Clinical pharmacology and therapeutics. 1962;3:184-90.	No RCT (allocation not randomised)
Pialoux P. Study of a programmed-release preparation of betahistidine mesulate in the treatment of Ménière's disease. Annales d'Oto-Laryngologie et de Chirurgie Cervico-Faciale. 1981;98(9):483-6.	Comparator out of scope (no 'placebo or no treatment' as control group)
Ramos Alcocer R, Ledezma Rodríguez JG, Navas Romero A, Cardenas Nuñez JL, Rodríguez Montoya V, Deschamps JJ, et al. Use of betahistine in the treatment of peripheral vertigo. Acta Otolaryngol. 2015;135(12):1205-11.	Narrative review
Redon C, Lopez C, Bernard-Demanze L, Dumitrescu M, Magnan J, Lacour M, et al. Betahistine treatment improves the recovery of static symptoms in patients with unilateral vestibular loss. Journal of Clinical Pharmacology. 2011;51(4):538-48.	Population out of scope (patients with Ménière's disease who underwent unilateral vestibular neurotomy)
Reker U. [Therapy of peripheral vestibular vertigo with betahistine dimesilate (Aequamen)]. MMW Munch Med Wochenschr. 1983;125(41):915-8.	No RCT
Salami A, Delle Piane M, Tinelli E, Jankowska B. Double blind study between betahistine hydrochloride and placebo in the treatment of Ménière's syndromes. Il Valsalva. 1984;60(3):302-12.	Inadequate data (incomplete data)
Savage J, Cook S, Waddell A. Tinnitus. BMJ clinical evidence. 2009;2009.	Systematic review
Savage J, Waddell A. Tinnitus. BMJ Clin Evid. 2012;2012.	Systematic review
Sayin I, Koç RH, Temirbekov D, Gunes S, Cirak M, Yazici ZM. Betahistine add-on therapy for treatment of subjects with posterior benign paroxysmal positional vertigo: a randomized controlled trial. Brazilian Journal of Otorhinolaryngology. 2022;88(3):421-6.	Population out of scope (patients with BPPV treated with betahistine)
Schmidt JT, Huizing EH. Betahistine dihydrochloride retard in Ménière's disease: a placebo-controlled, double-blind cross-over trial. The netherlands ENT society - abstracts of the 171st meeting held in may 1990 Clinical otolaryngology and allied sciences. 1991;16:104.	Irrelevant publication type (conference abstract)
Schmidt JT, Huizing EH. The clinical drug trial in Ménière's disease. With emphasis on the effect of betahistine SR. Acta Oto-Laryngologica, Supplement. 1992(497):5-181.	Narrative review
Segers JM. Initial findings in the treatment of Ménière's disease with betahistine hydrochloride (Betaserc). Acta oto-rhino-laryngologica Belgica. 1972;26(2):262-8.	Language out of scope (article in Dutch)
Segers JM, Boedts D. Clinical trials of betahistine hydrochloride in the treatment of Ménière's disease. Acta Oto-Rhino-Laryngologica Belgica. 1975;29(5):814-21.	No RCT
Sharif S, Khoujah D, Greer A, Naples JG, Upadhye S, Edlow JA. Vestibular suppressants for benign paroxysmal positional vertigo: A systematic review and meta-analysis of randomized controlled trials. Academic Emergency Medicine. 2023;30(5):541-51.	Systematic review
Singarelli S. Double-blind trial on the efficacy of betahistine hydrochloride in a group of outpatients with positional vertigo and tinnitus. Nuovo archivio italiano di otologia rinologia e laringologia. 1979:69-72.	No RCT (allocation not randomised)
Singh G, Aggarwal A, Sahni D, Kumar Sharma D, Yadav V, Bhagat S. Comparative Effectiveness Research: Betahistine add-on Therapy with Epley's Manoeuvre Versus Epley's Manoeuvre Alone in Treating Posterior BPPV Patients. Indian J Otolaryngol Head Neck Surg. 2023;75:204-9.	Population out of scope (patients with BPPV treated with betahistine)
Sollner B. First-line therapy in vertigo: Fixed combination of cinnarizine and dimenhydrinate shows superior efficacy. Journal fur Pharmakologie und Therapie. 2010;19(5):149-51.	Narrative review
Sönmez O, Külahli I, Vural A, Şahin MI, Aydin M. The evaluation of ozone and betahistine in the treatment of tinnitus. European Archives of Oto-Rhino-Laryngology. 2013;270(7):1999-2006.	Patients not randomised to control group
Stambolieva K, Angov G. Effect of treatment with betahistine dihydrochloride on the postural stability in patients with different duration of benign paroxysmal positional vertigo. International Tinnitus Journal. 2010;16(1):32-6.	Population out of scope (patients with BPPV treated with betahistine)
Ugurlu B, Evcimik MF, Ozkurt FE, Sapci T, Gursel AO. Comparison of the effects of betahistine dihydrochloride and brandt-daroff exercises in addition to epley maneuver in	Population out of scope (patients with BPPV treated with betahistine)

the treatment of benign paroxysmal positional vertigo. The Journal of International Advanced Otology. 2012;8(1):45.	
Van de Heyning P, Betka J, Chovanec M, Devèze A, Giannuzzi AL, Krempaská S, et al. Efficacy and Safety of Intranasal Betahistine in the Treatment of Surgery-Induced Acute Vestibular Syndrome: A Double-Blind, Randomized, Placebo-Controlled Phase 2 Study. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2023;44(5):493-501.	Population out of scope (patients with surgery-induced acute vestibular syndrome treated with betahistine)
Van Esch B, Van Der Zaag-Loonen H, Bruintjes T, Van Benthem PP. Betahistine in Ménière's Disease or Syndrome: A Systematic Review. Audiology and Neurotology. 2022;27(1):1-33.	Systematic review
Van Esch BF, Van der Zaag-Loonen H, Bruintjes T, Kuijpers T, Van Benthem PPG. Interventions for Menière's disease: an umbrella systematic review. BMJ evidence-based medicine. 2022;27(4):235-45.	Systematic review
Wang K, Rong L, Zhu B, Wang H, Xiao L. Epley maneuver associated with vertigo calming for treating posterior semicircular canal benign paroxysmal positional vertigo in young. Clinical Medicine of China. 2015:795-8.	Language out of scope (article in Chinese)
Watanabe K, Fukami J, Yoshimoto H, Ueda M, Suzuki J. Evaluation of the effect of betahistine in Ménière's disease by double-blind test and multivariate analysis. Jibi inkōka Otolaryngology. 1967;39(11):1237-50.	Language out of scope (article in Japanese)
Watanabe K, Fukami J, Yoshimoto H, Ueda M, Suzuki J, Okamato M. Evaluation of efficacy of betahistine on patients with vertigo by double blind test and discriminant analysis. Japanese medical news (overseas edition). 1967;119:3-9.	Language out of scope (article in Japanese)
Watanabe I, Saito H, Hinoki M, Naito T, Uemura T, Ushio N, et al. Comparative clinical study on effectiveness and safety of cinnarizine and betahistine on vertigo by double-blind trial test. Rinsho hyoka [clinical evaluation]. 1980;8(3):675-718.	Language out of scope (article in Japanese)
Webster KE, Galbraith K, Harrington-Benton NA, Judd O, Kaski D, Maarsingh OR, et al. Systemic pharmacological interventions for Ménière's disease. Cochrane Database of Systematic Reviews. 2023;2023(2).	Systematic review
Wegner I, Hall DA, Smit AL, McFerran D, Stegeman I. Betahistine for tinnitus. Cochrane Database of Systematic Reviews. 2018;2018(12).	Systematic review
Wilmot TJ. An objective study of the effect of betahistine hydrochloride on hearing and vestibular function tests in patients with Ménière's disease. The Journal of laryngology and otology. 1971;85(4):369-73.	No RCT
Wilmot TJ. The effect of betahistine hydrochloride in Méniére's disease. Acta oto-laryngologica Supplementum. 1972;305:18-21.	Duplicate article
Wolfson RJ, Myers D, Schlosser WD. Ménière's Disease - treatment with Betahistine Hydrochloride. Eye, ear, nose, throat monthly. 1967;46:891-6.	No RCT
Wu PX, Liu JP, Wang WQ, Li HW. Intervention strategies for residual dizziness after successful repositioning maneuvers in benign paroxysmal positional vertigo: a single center randomized controlled trial. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. 2021;56(1):41-6.	Language out of scope (article in Chinese)
yd3rg RBR. Effect of the Betahistine as a treatment for Tinnitus. https://trialsearchwhoint/Trial2aspx?TrialID=RBR-3yd3rg. 2019.	Irrelevant publication type (trial registry)
Yiannakis C, Hamilton L, Slim M, Kontorinis G. A systematic review and meta-analysis of prophylactic medication of vestibular migraine. Journal of Laryngology and Otology. 2023;137(9):953-61.	Systematic review
Zhang D, Li D, Wang Y, Zhang H. Study on the effect of acetyl gastrodin on residual dizziness after benign paroxysmal positional vertigo reduction. Acta Medica Mediterranea. 2020;36(2):1217-22.	Population out of scope (patients with BPPV treated with betahistine)

C. Summary figures risk of bias RCTs – RoB 2 tool

Betahistine for Ménière's disease

Figure 9. Summary risk of bias RCT on betahistine for Ménière's disease – vertigo attack frequency

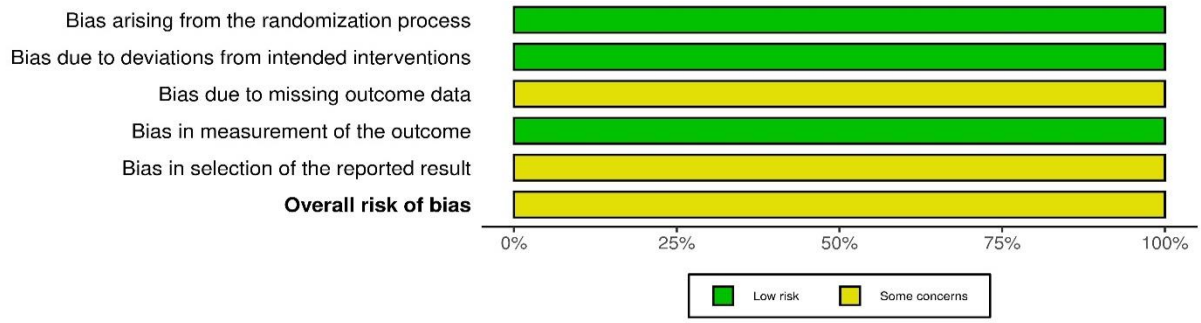


Figure 10. Summary risk of bias RCT on betahistine for Ménière's disease – tinnitus intensity

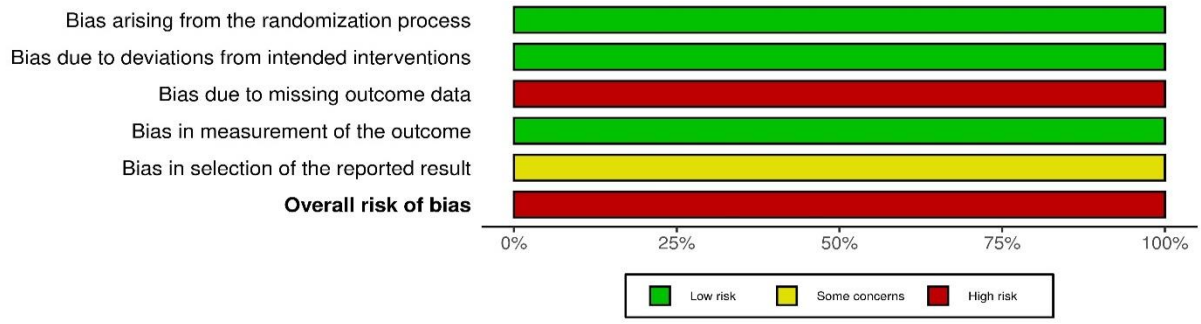


Figure 11. Summary risk of bias RCT on betahistine for Ménière's disease – hearing loss

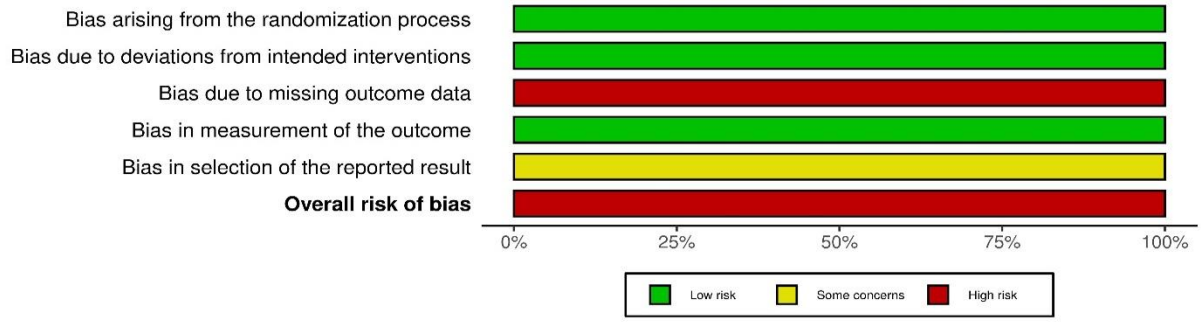


Figure 12. Summary risk of bias RCTs on betahistine for Ménière's disease – HRQoL assessed with DHI

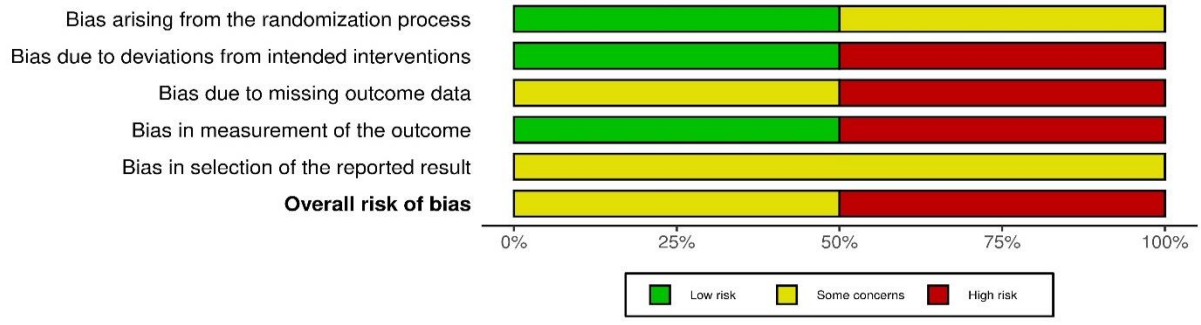


Figure 13. Summary risk of bias RCT on betahistine for Ménière's disease – HRQoL assessed with VDADL

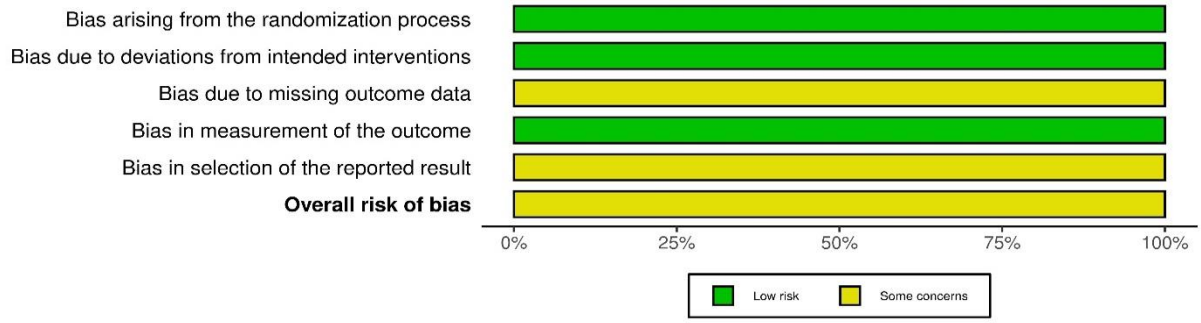


Figure 14. Summary risk of bias RCT on betahistine for Ménière's disease – HRQoL assessed with MiniTF12

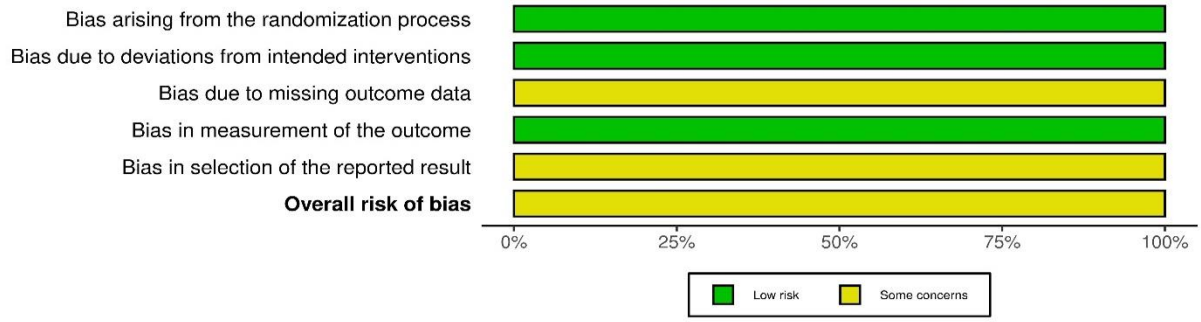
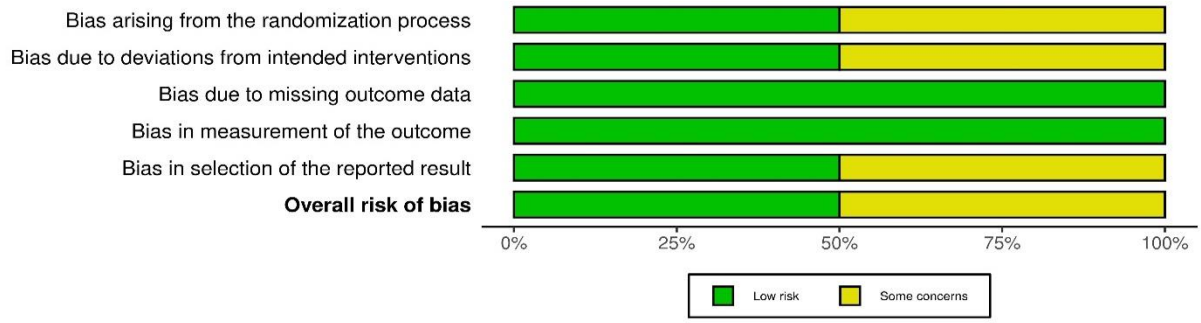


Figure 15. Summary risk of bias RCTs on betahistine for Ménière's disease – SAEs



Betahistine for vertigo

Figure 16. Summary risk of bias RCT on betahistine for vertigo – vertigo attack frequency and duration

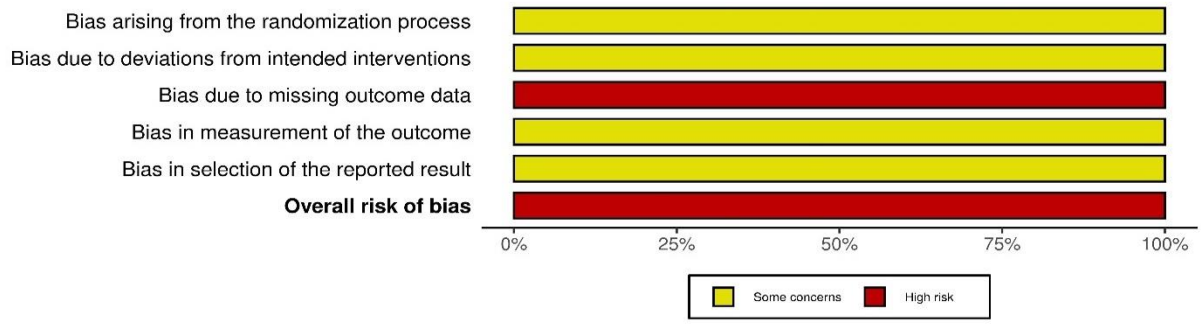


Figure 17. Summary risk of bias RCTs on betahistine for vertigo – vertigo attack severity

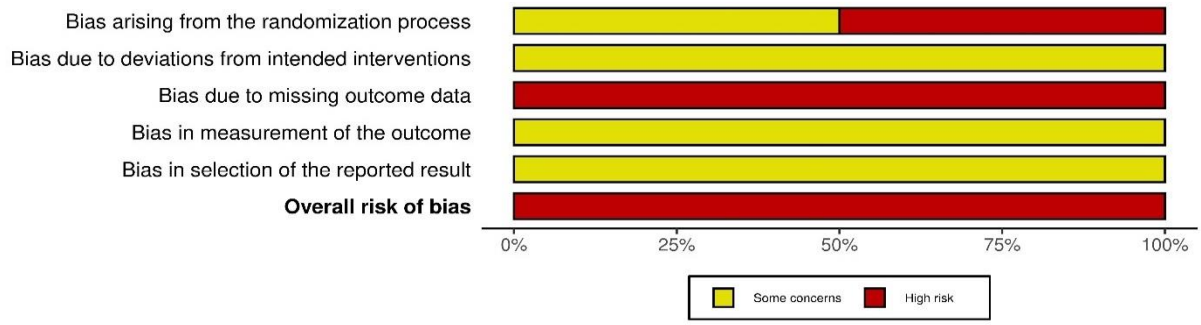


Figure 18. Summary risk of bias RCT on betahistine for vertigo – investigator-reported vertigo change

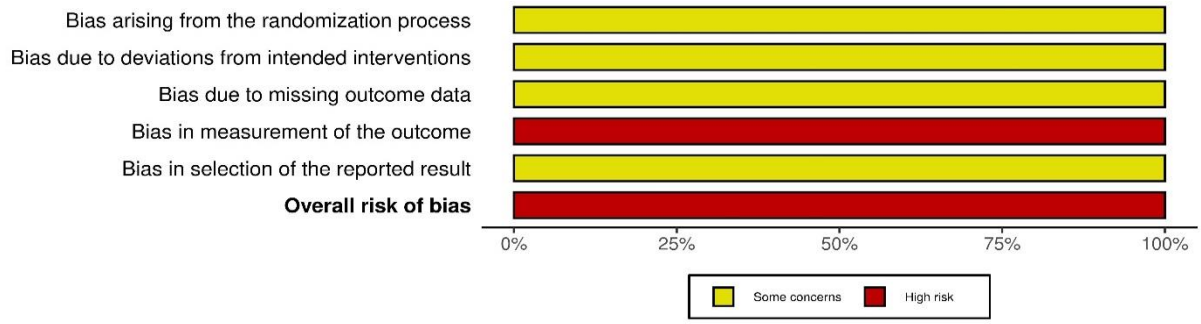
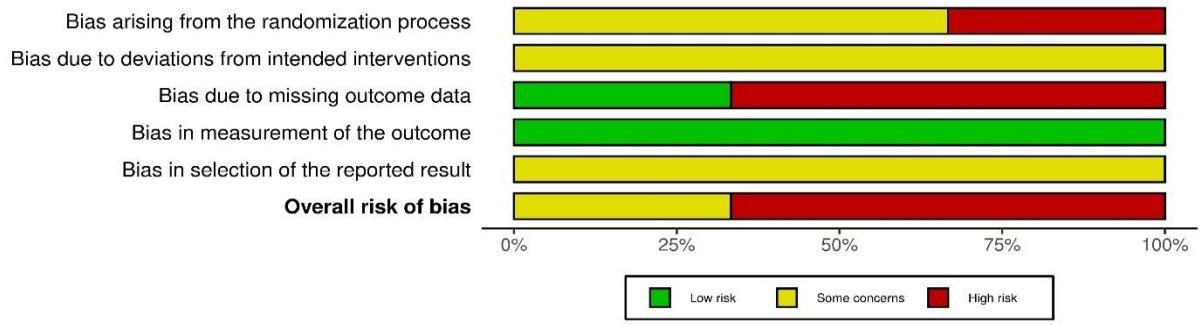


Figure 19. Summary risk of bias RCTs on betahistine for vertigo – SAEs



Cinnarizine for tinnitus

Figure 20. Summary risk of bias RCT on cinnarizine for tinnitus – tinnitus disturbance

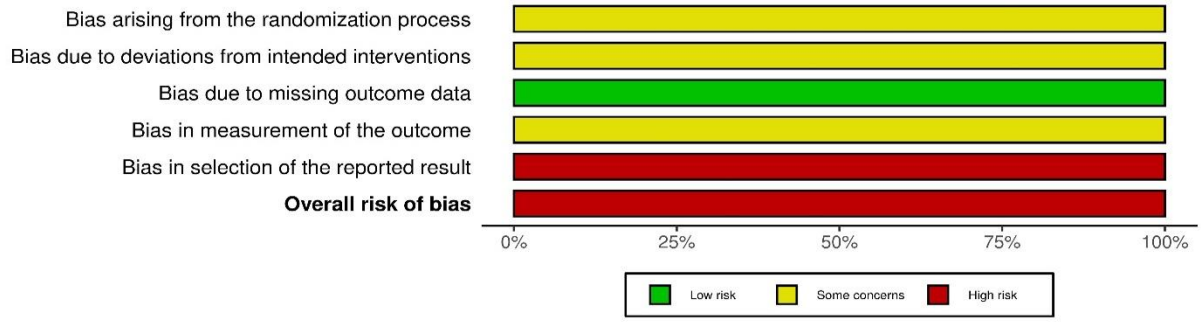
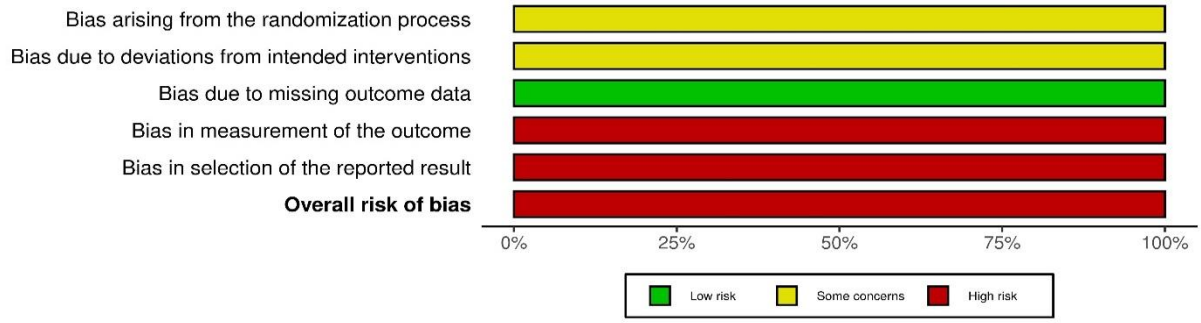


Figure 21. Summary risk of bias RCT on cinnarizine for tinnitus – patient-reported tinnitus change



Cinnarizine with dimenhydrinate for vertigo

Figure 22. Summary risk of bias RCTs on cinnarizine with dimenhydrinate for vertigo – mean vertigo score

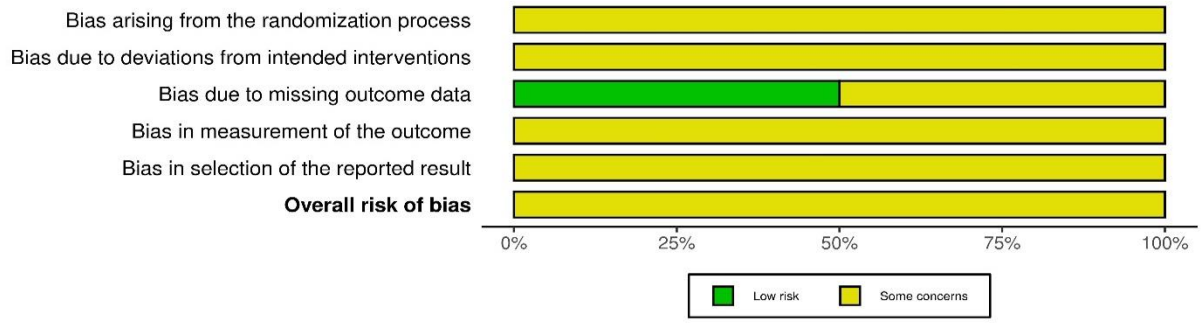


Figure 23. Summary risk of bias RCT on cinnarizine with dimenhydrinate for vertigo – patient and investigator-reported overall efficacy of treatment

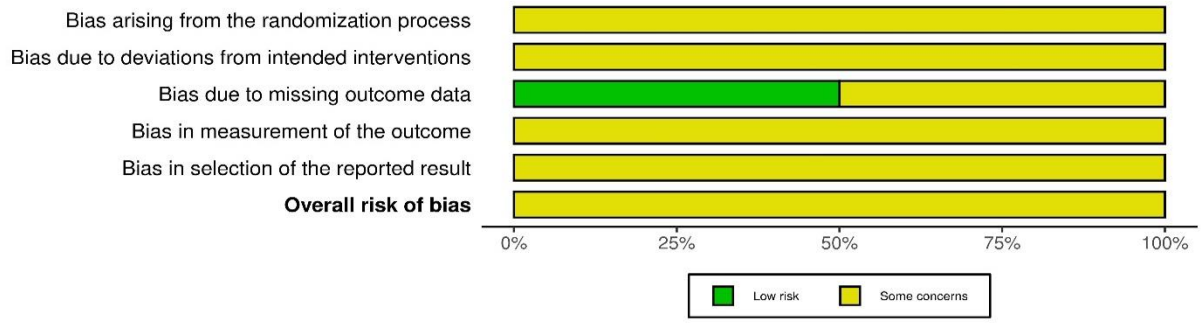
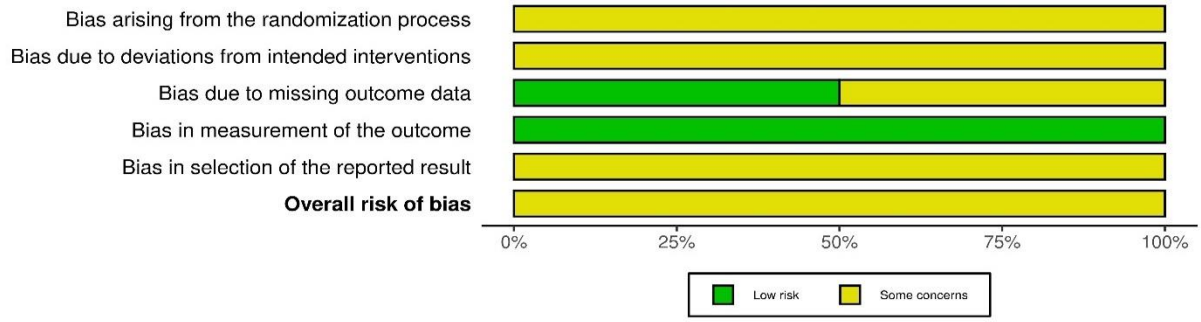


Figure 24. Summary risk of bias RCT on cinnarizine with dimenhydrinate for vertigo – SAEs



D. Summary tables of extracted results with missing data

Betahistine for Ménière's disease

Table 70. Efficacy results with missing data on betahistine for Ménière's disease – vertigo attack frequency

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD number attacks per month	p-value between group	Post-treatment mean±SD number attacks per month	p-value between group	Change attack frequency (95% CI)	Rate ratio (95% CI)	p-value between group
Mira et al 2003	Betahistine (32 mg/day; 3 months)	NR	6.70±9.56	NR	2.06±2.78	<0.05	~-63% (NR)	NR	NR
	Placebo (3 months)	NR	NR		NR		~-20% (NR)		

Abbreviations
CI = confidence interval, NR = not reported, SD = standard deviation.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 71. Efficacy results with missing data on betahistine for Ménière's disease – vertigo intensity

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD intensity score[a]	p-value between group	Post-treatment mean±SD intensity score[a]	p-value between group	% of patients improved	Rate ratio (95% CI)	p-value between group
Mira et al 2003	Betahistine (32 mg/day; 3 months)	NR	NR	NR	NR	NR	~66% (NR)	NR	NR
	Placebo (3 months)	NR	NR		NR		~31% (NR)		

Abbreviations
CI = confidence interval, NR = not reported, SD = standard deviation.
Notes
a = GISFaV self-rating scale for the determination of the disturbance stage of vertigo using values of intensity (V), duration (D) and associated symptoms (N) scored respectively by a 4-point scale (V: 0=absent, 1=mild, 2=severe, 3=disabling), 5-point scale (D: 0=none, 1=<1 min, 2=<15 min, 3=some hours, 4=≥1 day) and 3-point scale (N: 0= absent, 1=nausea, 2=vomiting).
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 72. Efficacy results on betahistine in patients with Ménière's disease – vertigo attack duration

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD	p-value between group	Post-treatment mean±SD	p-value between group	Estimate[a] months 7-9[b] (95% CI) versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	NR	NR	NR	NR	NR	-0.59 (-1.41 to 0.22)	0.348
	Betahistine high dose (144 mg/day; 9 months)	*NR*	*NR*		*NR*		*-0.38 (-1.21 to 0.44)*	
	Placebo (9 months)	NR	NR		NR		NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported.
Notes
a = Estimated coefficients with cumulative logit model, reported on the logit scale.
b = Assumption of a maximal effect of intervention during the prespecified 90-day assessment period (months 7-9).
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 73. Efficacy results on betahistine in patients with Ménière's disease – vertigo attack severity

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Pre-treatment mean±SD	p-value between group	Post-treatment mean±SD	p-value between group	Estimatea months 7-9b (95% CI) versus placebo	p-value between group
Adrion et al 2016	Betahistine low dose (48 mg/day; 9 months)	NR	NR	NR	NR	NR	-0.51 (-1.40 to 0.39)	0.390
	Betahistine high dose (144 mg/day; 9 months)	NR	NR		NR		0.06 (-0.82 to 0.94)	
	Placebo (9 months)	NR	NR		NR		NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported.
Notes
a = Estimated coefficients with cumulative logit model, reported on the logit scale.
b = Assumption of a maximal effect of intervention during the prespecified 90-day assessment period (months 7-9).
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 74. Efficacy results with missing data on betahistine for Ménière's disease – vertigo and hearing control

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Frequency vertigo attacks		Hearing loss		Vertigo and hearing control according AAOO 1972 criteria	
			Pre-treatment mean±SD number attacks per month	p-value between group	Pre-treatment	p-value between group	Class A-D[a] n (%) patients	p-value between group
Ricci et al 1987	Betahistine (24 mg/day; 10.4±1.2 months)	5	NR	NR	NR	NR	A: 1 (20.0%) B: 2 (40.0%) C: 0 (0%) D: 2 (40.0%)	NR
	Placebo (7.0±1.3 months)	5	NR		NR		A: 0 (0%) B: 0 (0%) C: 0 (0%) D: 5 (100%)	

Abbreviations
AAOO = American Academy of Ophthalmology and Otolaryngology, NR = not reported, SDS = speech discrimination score, SPTA = standard pure-tone average of speech frequencies, SRT = speech reception threshold.
Notes
a = Class A: Control of vertigo, Hearing improved (15 dB SPTA gain with SRT >30 dB or 15%, SDS gain with at least 80% discrimination score); Class B: Control of vertigo, Hearing unchanged; Class C: Control of vertigo, Hearing worse (15 dB SPTA loss or 15% SDS loss with 80% or less discrimination score), Class D: Failure of control of definitive spells.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 75. Efficacy results with missing data on betahistine for Ménière's disease – change in hearing

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Hearing loss		Change in hearing according ANSI			p-value between group
			Pre-treatment	p-value between group	Unchanged n (%) patients	Improved n (%) patients	Worsened n (%) patients	
Ricci et al 1987	Betahistine (24 mg/day; 10.4±1.2 months)	5	NR	NR	4 (80.0%)	1 (20.0%)	0 (0%)	NR
	Placebo (7.0±1.3 months)	5	NR		5 (100%)	0 (0%)	0 (0%)	

Abbreviations
ANSI = American National Standards Institute, ITD = intratympanic dexamethasone, NR = not reported.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 76. Efficacy results with missing data on betahistine for Ménière's disease – HRQoL assessed with DHI[a]

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD total score	p-value between group	Post-treatment mean±SD total score	p-value between group	Change in total severity score	p-value between group
Mira et al 2003	Betahistine (32 mg/day; 3 months)	NR	NR	NR	NR	NR	-40.2%	NR (<0.02 for combined population of Ménière's disease and PPV)
	Placebo (3 months)	NR	NR		NR		-28.1%	

Abbreviations
DHI = Dizziness handicap inventory, NR = not reported, PPV = paroxysmal positional vertigo, SD = standard deviation.
Notes
a = DHI comprises 25 items and assesses the impact of dizziness on emotional (9 items), functional (9 items), and physical (7 items) subdomains. There are 3 answers to each question: "yes" (=4 points), "sometimes" (=2 points), and "no" (=0 points). Total score ranges from 0 to 100; higher score is worse.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Table 77. Efficacy results with missing data on betahistine for Ménière's disease – HRQoL assessed with DARS[a]

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Pre-treatment mean±SD total score	p-value between group	Post-treatment mean±SD total score	p-value between group	Change in total score	p-value between group
Mira et al 2003	Betahistine (32 mg/day; 3 months)	NR	NR	NR	NR	NR	-66.7%	NR (<0.00001 for combined population of Ménière's disease and PPV)
	Placebo (3 months)	NR	NR		NR		-31.2%	

Abbreviations
DARS = dizziness assessment rating scale, NR = not reported, PPV = paroxysmal positional vertigo, SD = standard deviation.
Notes
a = DARS consists of 6 entries: Disequilibrium (standing), Disequilibrium (walking), Dizziness (now), Dizziness (past week), Feeling confused or disoriented, Global impression (physician), Global impression (patient). Each includes 7 levels: 0=none, 1=very mild, 2=mild, 3=mild to moderate, 4=moderate, 5=moderate to severe, 6=severe. The total score ranges from 0 to 36; higher score is worse.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Betahistine for vertigo

Table 78. Efficacy results with missing data on betahistine for vertigo – vertigo remission

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Number of vertigo attacks		Good results[a] on monthly number of vertigo attacks		In remission	
			Pre-treatment mean±SD	p-value between group	Post-treatment n (%) patients	p-value between group	Post-treatment n (%) patients	p-value between group
Conraux et al 1988	Betahistine (close to 48 mg/day; 3 months)	27	NR	NR	~23 (85%)	0.006	9 (33%)	NR
	Placebo (3 months)	20	NR		~14 (70%)		3 (15%)	

Abbreviations
~ = approximate estimation extracted from figure, NR = not reported, SD = standard deviation.
Notes
a = Good results are defined as patients in remission or improvement, i.e. having a lower number of vertigo attacks recorded at each examination than at the initial examination.
*Data on off-label betahistine use will be described in **Section 9.4**.*

Cinnarizine for tinnitus

Table 79. Efficacy results with missing data on cinnarizine for tinnitus – tinnitus assessed with speech reception threshold[a]

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Pre-treatment mean±SD in dB	p-value between group	Post-treatment mean±SD in dB	p-value between group	Change	p-value between group
Podoshin et al 1991	Cinnarizine (75 mg/day; 10 weeks)	10	NR	NR	27±19	NR	NR	NR
	Placebo (10 weeks)	20	NR		30±22		NR	

Abbreviations
NR = not reported, SD = standard deviation.
Notes
a = Tinnitus was objectively evaluated using a matching technique by which the frequency and intensity of the tinnitus sensation of the patients was compared to the tones of audiometers.

E. Summary tables of RCTs on off-label betahistine use for Ménière's disease

Table 80. Study characteristics – off-label betahistine use for Ménière's disease

Reference	Study design; setting Funding	Country Study period	Study population Study arm	Sample size randomised	Age (mean±SD)	Sex (% male)	Comorbidities n (%)	Comedication n (%)	Diagnosis, unilateral or bilateral (definition) Exclusion criteria related to diagnosis	Intervention - brand name - dose - treatment duration
Adrion et al 2016	Parallel RCT; multicentre Non-industry funded	Germany March 2008-Nov 2013	Patients aged 18-80 years with Ménière's disease and ≥2 vertigo attacks/ month in ≥3 months before study						Definite Ménière's disease, unilateral or bilateral (AAO-HNS 1995 criteria) Other central or peripheral vestibular disorders, e.g. vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, phobic postural vertigo	Betahistine - Vasomotal - *low dose: 48 mg/day (24 mg bid)* - high dose: 144 mg/day (48 mg tid) - 9 months
			Betahistine low dose	*73*	*56.1±11.1 years*	*53%*	history of migraine: 9 (12%)	NR[a]		
			Betahistine high dose	74	56.1±12.6 years	47%	*history of migraine: 13 (18%)*	*NR*[a]		
			Placebo	74	54.5±12.8 years	47%	history of migraine: 17 (23%)	NR[a]		
Albu et al 2016	Parallel RCT; multi centre Not funded	Romania, Italy Jan 2009-June 2013	Adult patients with Ménière's disease and ≥4 vertigo attacks/month during 3 months before study						Definite Ménière's disease, unilateral (AAO-HNS 1995 criteria) Bilateral, possible or probable Ménière's disease; other peripheral or central vestibular syndromes, middle ear pathology, noise-induced hearing loss	Betahistine + ITD[b] - NR - 144 mg/day (48 mg tid) - 24 months
			Betahistine + ITD[b]	33	NR	45%	NR	ITD: 33 (100%)		
			Placebo + ITD[b]	33	NR	36%	NR	ITD: 33 (100%)		

Abbreviations
AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery, bid = bis in die (twice a day), ITD = intratympanic dexamethasone, NR = not reported, SD = standard deviation, tid = ter in die (3 times a day).
Notes
a = There were no disallowed concomitant drugs used during the study except for antihistaminic drugs, because the researchers aimed to assess the efficacy of the assigned prophylactic treatment irrespective of rescue medication use by measuring efficacy conditional on real life adherence. Hence, rescue medication for managing of acute vertigo related symptoms such as vomiting or nausea could also be prescribed, because a possible effect on the occurrence of vertigo attacks is unknown.
b = One injection with ITD (4 mg); if complete or substantial vertigo control was not accomplished with ITD, another sequence of ITD (4 mg) was offered. In betahistine + ITD group: 4 (12%) patients received 1 ITD reinjection and 3 (9%) patients received 2 re-injections. In placebo + ITD group: 5 (15%) patients received 1 ITD reinjection and 6 (18%) patients received 2 re-injections.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 81. Efficacy results on off-label betahistine use for Ménière's disease – vertigo attack frequency, duration and severity

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Vertigo attack frequency									Vertigo attack duration		Vertigo attack severity	
			Pre-treatment mean±SD number attacks per month	p-value between group	Post-treatment months 7-9[a] mean (95% CI) number attacks per month	p-value between group	Adjusted monthly decay rate (95% CI) attacks over 9 months	Adjusted rate ratio (95% CI) over 9 months versus placebo	p-value between group	Adjusted rate ratio (95% CI) months 7-9[a] versus placebo	p-value between group	Estimate[b] months 7-9[a] (95% CI) versus placebo	p-value between group	Estimate[b] months 7-9[a] (95% CI) versus placebo	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*NR*	*5.8±4.6[c]*	0.625	*3.20 (1.35 to 7.93)*	NR	*NR*	*1.04 (0.94 to 1.14)*	0.759	*0.85 (0.47 to 1.53)*	0.850	*-0.59 (-1.41 to 0.22)*	0.348	*-0.51 (-1.40 to 0.39)*	0.390
	Betahistine high dose (144 mg/day; 9 months)	NR	5.1±4.5[c]		3.26 (1.69 to 7.27)		NR	1.01 (0.92 to 1.11)		0.89 (0.49 to 1.63)		-0.38 (-1.21 to 0.44)		0.06 (-0.82 to 0.94)	
	Placebo (9 months)	NR	6.2±6.9[c]		2.72 (1.30 to 6.31)		0.76 (0.71 to 0.82)	NA		NA		NA		NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = Assumption of a maximal effect of intervention during the prespecified 90-day assessment period (months 7-9).
b = Estimated coefficients with cumulative logit model, reported on the logit scale.
c = Pseudobaseline data reported for n=69 betahistine low dose, n=69 betahistine high dose and n=66 placebo. Pseudobaseline data is data documented during the first treatment month (with day 1 being the day of first study drug intake); pre-treatment attack data was not available.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 82. Efficacy results on off-label betahistine use for Ménière's disease – vertigo control

Reference	Intervention (dose; duration)	Sample size analysed	Frequency vertigo attacks		Vertigo control[a] according AAO-HNS 1995 criteria					
	Comparator (duration)		Pre-treatment mean±SD number attacks per month	p-value between group	Class A-E[a] n (%) patients	p-value between group	Class A (complete vertigo control) n (%) patients	p-value between group	Class A+B (substantial vertigo control) n (%) patients	p-value between group
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	6.7±NR	Not significant (p NR)	A: 22 (73.3%) B: 5 (16.6%) C: 1 (3.3%) D: 1 (3.3%) E: 1 (3.3%)	0.11	A: 22 (73.3%)	0.01[b] 0.027[c]	A+B: 27 (90.0%)	0.02[b] 0.035[c]
	Placebo + ITD (24 months)	32	7.5±NR		A: 14 (43.8%) B: 7 (21.9%) C: 6 (18.8%) D: 4 (12.5%) E: 1 (3.1%)		A: 14 (43.8%)		A+B: 21 (65.6%)	

Abbreviations
AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery, AAOO = American Academy of Ophthalmology and Otolaryngology, ITD = intratympanic dexamethasone, NR = not reported, SDS = speech discrimination score, SPTA = standard pure-tone average of speech frequencies, SRT = speech reception threshold.
Notes
a = Class A: Complete control (control level 0); Class B: Substantial control (control level 1-40); Class C: Limited control (control level 41-80); Class D Insignificant control (control level 81-120); Class E: Worsened (control level >120). Control level is calculated as (average vertigo attacks per month post-treatment/average vertigo attacks per month pre-treatment) x 100.
b = Chi-square test.
c = Log rank test Kaplan-Meier plot.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 83. Efficacy results on off-label betahistine use for Ménière's disease – tinnitus intensity

Reference	Intervention (dose; duration) / Comparator (duration)	Sample size analysed	Tinnitus intensity assessed with pure tone audiometry							Tinnitus Handicap Inventory (THI)[a]				
			Pre-treatment mean±SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[b] versus placebo (dB)	p-value between group	Pre-treatment mean±SD	p-value between group	Post-treatment mean±SD	p-value between group	p-value within-group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*24*	*44.5±22.8*[c]	NR	*+7.07 (0.53 to 13.60)*	0.107	*NR*	*+1.40 (-5.10 to 7.90)*	0.338	-	-	-	-	-
	Betahistine high dose (144 mg/day; 9 months)	28	54.0±19.8[c]		-1.82 (-7.96 to 4.31)		NR	-3.34 (-9.74 to 3.06)		-		-		-
	Placebo (9 months)	35	42.8±22.0[c]		-0.56 (-6.02 to 4.91)		+6.82 (-0.34 to 13.99)	NA		-		-		-
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	-	-	-	-	-	-	-	28.3±14.8	0.81	26.3±12.7	0.72	0.46
	Placebo + ITD (24 months)	32	-		-		-	-		27.7±16.7		25.4±13.2		0.31

Abbreviations
CI = confidence interval, ITD = intratympanic dexamethasone, NA = not applicable, NR = not reported, SD = standard deviation, THI = tinnitus handicap inventory.
Notes
a = THI is a 25-item questionnaire to assess the severity of tinnitus. Each item is completed with "yes" (=4 points), "sometimes" (=2 points), and "no" (=0 points); higher score is worse.
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment tinnitus intensity reported for n=40 betahistine low dose, n=45 betahistine high dose and n=50 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 84. Efficacy results on off-label betahistine use for Ménière's disease – hearing loss

Reference	Intervention (dose; duration)	Sample size analysed	Pure tone audiometry (PTA) 250 Hz							Pure tone audiometry (PTA) 500 Hz						
	Comparator (duration)		Pre-treatment mean±SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo in (dB)	p-value between group	Pre-treatment mean± SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo (dB)	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*40[b]; 46[c]*	*32.8±16.0[d]*	*NR*	*-1.99 (-5.20 to 1.22)*	0.316	*NR*	*+0.33 (-3.13 to 3.79)*	0.954	*36.5±19.2[e]*	NR	*+0.29 (-3.64 to 4.21)*	0.231	*NR*	*+1.99 (-2.64 to 6.62)*	0.597
	Betahistine high dose (144 mg/day; 9 months)	39[b]; 48[c]	29.6±16.0[d]		-2.88 (-6.12 to 0.35)		NR	-0.21 (-3.86 to 3.43)		35.4±19.9[e]		-3.27 (-7.10 to 0.56)		NR	-0.08 (-4.51 to 4.35)	
	Placebo (9 months)	34[b]; 44[c]	29.4±18.2[d]		-5.53 (-9.01 to -2.06)		+4.75 (1.04 to 8.45)	NA		33.6±20.0[e]		-4.37 (-8.39 to -0.36)		+4.94 (0.41 to 9.47)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, PTA = pure tone audiometry, SD = standard deviation.
Notes
a = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
b = Sample size analysed for PTA 250 Hz.
c = Sample size analysed for PTA 500 Hz.
d = Pre-treatment PTA 250 Hz reported for n=51 betahistine low dose, n=55 betahistine high dose and n=54 placebo.
e = Pre-treatment PTA 500 Hz reported for n=58 betahistine low dose, n=64 betahistine high dose and n=60 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 85. Efficacy results on off-label betahistine use for Ménière's disease – hearing loss continued

Reference	Intervention (dose; duration)	Sample size analysed	Pure tone audiometry (PTA) 1000 Hz							Pure tone audiometry (PTA) 2000 Hz						
	Comparator (duration)		Pre-treatment mean± SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo in (dB)	p-value between group	Pre-treatment mean± SD (dB)	p-value between group	Mean absolute change (95% CI) month 9-baseline (dB)	p-value between group	Adjusted mean change (95% CI)[a] month 9-baseline (dB)	Adjusted treatment differences (95% CI)[a] versus placebo (dB)	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*49[b]; 51[c]*	*37.6±19.7[d]*	NR	*-0.60 (-4.29 to 3.09)*	0.196	*NR*	*+2.83 (-1.93 to 7.59)*	0.474	*38.7±19.3[e]*	NR	*+0.61 (-2.58 to 3.80)*	0.513	*NR*	*+1.67 (-2.41 to 5.74)*	0.504
	Betahistine high dose (144 mg/day; 9 months)	48[b]; 49[c]	34.4±21.3[d]		-2.96 (-6.68 to 0.77)		NR	+1.15 (-3.27 to 5.56)		37.9±18.5[e]		-1.84 (-5.10 to 1.42)		NR	-0.68 (-4.75 to 3.39)	
	Placebo (9 months)	47[b]; 45[c]	35.3±20.7[d]		-5.44 (-9.21 to -1.68)		+4.34 (-0.34 to 9.01)	NA		35.8±19.9[e]		-1.53 (-4.94 to 1.87)		+5.48 (1.30 to 9.66)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, PTA = pure tone audiometry, SD = standard deviation.
Notes
a = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
b = Sample size analysed for PTA 1000 Hz.
c = Sample size analysed for PTA 2000 Hz.
d = Pre-treatment PTA 1000 Hz reported for n=65 betahistine low dose, n=65 betahistine high dose and n=63 placebo.
e = Pre-treatment PTA 2000 Hz reported for n=65 betahistine low dose, n=64 betahistine high dose and n=62 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 86. Efficacy results on off-label betahistine use for Ménière's disease – change in hearing

Reference	Intervention (dose; duration)	Sample size analysed	Frequency average pure tone audiometry (PTA)[a]					Change in hearing according AAO-HNS 1995 criteria			
	Comparator (duration)		Pre-treatment mean±SD (dB)	p-value be-tween group	Post-treatment mean±SD (dB)	p-value be-tween group	p-value within-group	Unchanged n (%) patients	Improved n (%) patients	Worsened n (%) patients	p-value be-tween group
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	54.6±15.2	0.47	51.2±17.4	0.65	0.73	16 (53%)	2 (7%)	12 (40%)	NR
	Placebo + ITD (24 months)	32	51.4±13.6		49.8±16.7		0.38	15 (47%)	3 (9%)	14 (44%)	

Abbreviations
AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery, ITD = intratympanic dexamethasone, NR = not reported, SD = standard deviation.
Notes
a = Auditory testing comprised PTA with 4 frequency average (0.5, 1, 2, and 3 kHz). A change of ≥10 dB was considered clinically significant.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 87. Efficacy results on off-label betahistine use for Ménière's disease – hearing assessed with SDS

Reference	Intervention (dose; duration)	Sample size ana-lysed	Speech discrimination score (SDS)[a]				
	Comparator (duration)		Pre-treatment mean±SD	p-value be-tween group	Post-treatment mean±SD	p-value be-tween group	p-value within-group
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	68.4±17.7%	0.73	66.4±20.2%	0.68	0.54
	Placebo + ITD (24 months)	32	65.2±18.6%		63.6±19.8%		0.73

Abbreviations
ITD = intratympanic dexamethasone, SD = standard deviation, SDS = speech discrimination score.
Notes
a = To measure the SDS the patient listens to and repeats monosyllable words spoken by the examiner; the correct answer rate (in %) is output as the final score. A change of ≥15% in SDS was considered clinically significant.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 88. Efficacy results on off-label betahistine use for Ménière's disease – HRQoL assessed with DHI

Reference	Intervention (dose; duration)	Sample size analysed	Dizziness handicap inventory (DHI)[a] mean total score, averaging the number of available answers							Dizziness handicap inventory (DHI)[a] mean total score				
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group	Pre-treatment mean±SD	p-value between group	Post-treatment mean±SD	p-value between group	p-value within-group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*57*	*1.78±1.01*[c]	NR	*-0.36 (-0.55 to -0.17)*	0.482	*NR*	*+0.08 (-0.17 to 0.33)*	0.666	-	-	-	-	-
	Betahistine high dose (144 mg/day; 9 months)	57	1.77±0.91[c]		-0.52 (-0.71 to -0.33)		NR	-0.03 (-0.27 to 0.22)		-		-		-
	Placebo (9 months)	56	1.69±0.90[c]		-0.50 (-0.69 to -0.31)		-0.10 (-0.35 to 0.15)	NA		-		-		-

Abbreviations
CI = confidence interval, DHI = dizziness handicap inventory, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = DHI comprises 25 items and assesses the impact of dizziness on emotional (9 items), functional (9 items), and physical (7 items) subdomains. There are 3 answers to each question: "yes" (=4 points), "sometimes" (=2 points), and "no" (=0 points). Total score ranges from 0 to 100; higher score is worse.
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment DHI reported for n=68 betahistine low dose, n=74 betahistine high dose and n=72 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 89. Efficacy results on off-label betahistine use for Ménière's disease – HRQoL assessed with FLS

Reference	Intervention (dose; duration)	Sample size analysed	Functional level score (FLS)[a]			
	Comparator (duration)		Pre-treatment n (%) patients	p-value between group	Post-treatment n (%) patients	p-value between group
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	1: 0 (0%) 2: 0 (0%) 3: 5 (15%) 4: 15 (45%) 5: 13 (39%) 6: 0 (0%)	0.87	1: 22 (73%) 2: 7 (23%) 3: 1 (3%) 4: 0 (0%) 5: 0 (0%) 6: 0 (0%)	0.04
	Placebo + ITD (24 months)	32	1: 0 (0%) 2: 0 (0%) 3: 4 (12%) 4: 17 (52%) 5: 12 (36%) 6: 0 (0%)		1: 15 (47%) 2: 8 (25%) 3: 7 (22%) 4: 2 (6%) 5: 0 (0%) 6: 0 (0%)	

Abbreviations
FLS = functional level score, ITD = intratympanic dexamethasone.
Notes
a = FLS is a 6-point scale, for which patients check the scale that best applies to them regarding their current state of overall function, not just during attacks: 1=My dizziness has no effect on my activities at all; 2=When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.; 3=When I am dizzy I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.; 4=I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.; 5=I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.; 6=I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 90. Efficacy results on off-label betahistine use for Ménière's disease – HRQoL assessed with VDADL

Reference	Intervention (dose; duration) Comparator (duration)	Sample size analysed	Vestibular disorders activities of daily living (VDADL)[a] total score, averaging the number of available answers Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*58*	*1.75±1.53*[c]	NR	*-0.26 (-0.46 to -0.06)*	0.547	*NR*	*-0.05 (-0.32 to 0.22)*	0.883
	Betahistine high dose (144 mg/day; 9 months)	58	1.78±1.07[c]		-0.36 (-0.56 to -0.16)		NR	-0.06 (-0.33 to 0.20)	
	Placebo (9 months)	57	1.77±1.35[c]		-0.20 (-0.41 to 0.00)		+0.79 (0.53 to 1.06)	NA	

Abbreviations
CI = confidence interval, NA = not applicable, NR = not reported, SD = standard deviation, VDADL = vestibular disorders activities of daily living.
Notes
a = VDADL consists of 28 questions that assess subjects' comfort and ability to perform activities categorised as functional (F), ambulatory (A) and instrumental (I), and a total scale that summarises all 3 categories. Subjects score their responses to each question using integer numbers ranging from 1 (best) to 10 (worst).
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment VDADL reported for n=69 betahistine low dose, n=74 betahistine high dose and n=73 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 91. Efficacy results on off-label betahistine use for Ménière's disease – HRQoL assessed with MiniTF12

Reference	Intervention (dose; duration)	Sample size analysed	Mini-tinnitus impairment questionnaire (MiniTF12)[a] mean total score, averaging the number of available answers						
	Comparator (duration)		Pre-treatment mean±SD	p-value between group	Mean absolute change (95% CI) month 9-baseline	p-value between group	Adjusted mean change (95% CI)[b] month 9-baseline	Adjusted treatment differences (95% CI)[b] versus placebo	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*58*	*0.81±0.53*[c]	NR	*-0.11 (-0.21 to -0.01)*	0.929	*NR*	*-0.007 (-0.14 to 0.13)*	0.97
	Betahistine high dose (144 mg/day; 9 months)	56	0.73±0.48[c]		-0.14 (-0.24 to -0.04)		NR	-0.016 (-0.15 to 0.11)	
	Placebo (9 months)	54	0.77±0.56[c]		-0.12 (-0.22 to -0.02)		+0.07 (-0.05 to 0.18)	NA	

Abbreviations
CI = confidence interval, MiniTF12 = mini-tinnitus impairment questionnaire, NA = not applicable, NR = not reported, SD = standard deviation.
Notes
a = MiniTF12 contains selected 12 items from the full tinnitus questionnaire, which reflect most central and characteristic aspects: 5. I am aware of the noises from the moment I get up to the moment I sleep; 16. Because of the noises I worry that there is something seriously wrong with my body; 17. If the noises continue my life will not be worth living; 24. I am more irritable with my family and friends because of the noises; 28. I worry that the noises might damage my physical health; 34. I find it harder to relax because of the noises; 35. My noises are often so bad that I cannot ignore them; 36. It takes me longer to get sleep because of the noises; 39. I am more liable to feel low because of the noises; 43. I often think about whether the noises will ever go away; 47. I am a victim of my noises; 48. The noises have affected my concentration. Each item can be answered as either "true" (=2 points), "partly true" (=1 point) or "not true" (=0 points). Total score ranges from 0 to 24; higher score is worse.
b = ANCOVA for absolute change, with factor for treatment group (placebo used as reference category) and baseline value of the dependent variable used as a covariate. Multiple imputation techniques applied to deal with missing data (MICE approach; 21 imputed datasets created). Pooled p-values result from global testing (model with versus without treatment group).
c = Pre-treatment MiniTF12 reported for n=69 betahistine low dose, n=74 betahistine high dose and n=72 placebo.
*Data on licensed betahistine use is described in **Chapter 6**.*

Table 92. Safety results on off-label betahistine use for Ménière's disease – SAEs and other adverse events

Reference	Intervention (dose; duration)	Sample size analysed	Serious adverse events		Other adverse events			
	Comparator (duration)		≥1 SAE n (%) patients	p-value between group	Headache n (%) patients	p-value between group	Gastrointestinal disturbance n (%) patients	p-value between group
Adrion et al 2016	*Betahistine low dose (48 mg/day; 9 months)*	*72*	*12 (17%)*	*NR*	-	-	-	-
	Betahistine high dose (144 mg/day; 9 months)	74	14 (19%)		-		-	
	Placebo (9 months)	74	11 (15%)		-		-	
Albu et al 2016	Betahistine + ITD (144 mg/day; 24 months)	30	0%	NR	5 (17%)	NR	nausea: 2 (7%) diarrhoea: 8 (27%)	NR
	Placebo + ITD (24 months)	32	NR		NR		NR	

Abbreviations
ITD = intratympanic dexamethasone, NR = not reported, SAE = serious adverse event.
Notes
*Data on licensed betahistine use is described in **Chapter 6**.*

F. Search strategy economic systematic literature search

Table 93. PubMed (MEDLINE), primary systematic literature search

Population	"Meniere Disease"[Mesh] OR meniere*[tiab] OR "Vertigo"[Mesh] OR vertigo*[tiab] OR "Tinnitus"[Mesh] OR tinnitus[tiab]
Intervention	"Betahistine"[Mesh] OR "Cinnarizine"[Mesh] OR acuver*[tiab] OR am-125[tiab] OR am-201[tiab] OR am125[tiab] OR am201[tiab] OR antivom*[tiab] OR behistep*[tiab] OR bestin*[tiab] OR betabare*[tiab] OR betabire*[tiab] OR betagen*[tiab] OR betahecon*[tiab] OR betahistin*[tiab] OR beta-histin*[tiab] OR betalune*[tiab] OR betaserc*[tiab] OR betaserk*[tiab] OR fortamid*[tiab] OR histigen*[tiab] OR lectil[tiab] OR marac[tiab] OR marak[tiab] OR meniserc*[tiab] OR microser*[tiab] OR neatin*[tiab] OR pt-9[tiab] OR serc[tiab] OR sinmenier*[tiab] OR vasomotal*[tiab] OR vertiserc*[tiab] OR aplactan*[tiab] OR aplexal*[tiab] OR apomitere*[tiab] OR apotomin*[tiab] OR artate*[tiab] OR carecin*[tiab] OR cerebolan*[tiab] OR cerepar*[tiab] OR cibine*[tiab] OR cimarizine*[tiab] OR cinabioquim*[tiab] OR cinaperazine*[tiab] OR cinazyn*[tiab] OR cinnabene*[tiab] OR cinnacet*[tiab] OR cinnaforte*[tiab] OR cinnageron*[tiab] OR cinnarazin*[tiab] OR cinnarizin*[tiab] OR cinarizin*[tiab] OR cinnipirine*[tiab] OR cinniprine*[tiab] OR corathiem*[tiab] OR denapol*[tiab] OR dimitron*[tiab] OR dimitronal*[tiab] OR eglen*[tiab] OR giganten*[tiab] OR glanil*[tiab] OR hilactan*[tiab] OR ixertol*[tiab] OR katoseran*[tiab] OR labyrin[tiab] OR lazeta*[tiab] OR marisan*[tiab] OR md-516*[tiab] OR 516-md[tiab] OR midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r516[tiab] OR roin[tiab] OR sedatromin*[tiab] OR sepan*[tiab] OR siptazin*[tiab] OR spaderizine*[tiab] OR stugeron*[tiab] OR stutgeron*[tiab] OR stutgin*[tiab] OR arlevert*[tiab]
Comparator	No search string
Outcome	“Technology Assessment, Biomedical”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Quality-Adjusted Life Years”[Mesh] OR “technology assessment” [tiab] OR “economic evaluation” [tiab] OR “economic value” [tiab] OR “cost-benefit” [tiab] OR “cost-effective” [tiab] OR “cost-effectiveness” [tiab] OR “cost-utility” [tiab] OR “cost-consequence” [tiab] OR “quality-adjusted life year” [tiab] OR “QALY” [tiab]
Limits	No conference abstracts and preprints: NOT (congress[pt] OR preprint[pt])
Search date	14 November 2023

Table 94. Embase.com, primary systematic literature search

Population	'Meniere disease'/exp OR meniere*:ti,ab OR 'vertigo'/exp OR vertigo*:ti,ab OR 'tinnitus'/exp OR tinnitus:ti,ab
Intervention	'betahistine'/exp OR 'cinnarizine'/exp OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516-md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r516:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab
Comparator	No search string
Outcome	'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti
Limits	No conference abstracts/select other publication types: ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
Search date	14 November 2023

Table 95. Cochrane Library, primary systematic literature search

Population	[mh "Meniere Disease"] OR meniere*:ti,ab OR [mh Vertigo] OR vertigo*:ti,ab OR [mh Tinnitus] OR tinnitus:ti,ab
Intervention	[mh Betahistine] OR [mh Cinnarizine] OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r516:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab
Comparator	No search string
Outcome	[mh "Technology Assessment, Biomedical"] OR [mh "Cost-Benefit Analysis"] OR [mh "Quality-Adjusted Life Years"] OR technology assessment*:ti,ab OR economic evaluat*:ti,ab OR economic value:ti,ab OR cost-benefit*:ti,ab OR cost-effectiv*:ti,ab OR cost-efficien*:ti,ab OR cost-efficac*:ti,ab OR cost-minim*:ti,ab OR cost-utilit*:ti,ab OR cost-consequen*:ti,ab OR quality-adjusted life-year*:ti,ab OR quality-adjusted lifeyear*:ti,ab OR qaly*:ti,ab
Limits	No conference abstracts and preprints: NOT (congress:pt OR preprint:pt)
Search date	14 November 2023

Table 96. Tufts Medical Centre Cost-Effectiveness Analysis Registry and international HTA database, primary systematic literature search

Population	meniere OR vertigo OR tinnitus
Intervention	betahistine OR cinnarizine
Comparator	No search string
Outcome	No search string
Limits	Language: English, French, German, Italian
Search date	14 November 2023

Table 97. PubMed (MEDLINE), additional systematic literature search

Betahistine and specific conditions	(vestibular migraine[tiab] OR "Vertebrobasilar Insufficiency"[Mesh] OR vertebrobasilar insufficienc*[tiab] OR vertebro-basilar insufficienc*[tiab] OR vertebrobasilar ischemia[tiab] OR vertebro-basilar ischemia[tiab] OR "Ischemic Attack, Transient"[Mesh] OR transient ischemic attack*[tiab] OR TIA[tiab] OR TIAs[tiab] OR (anterior inferior cerebellar artery[tiab] AND infarct*[tiab]) OR (anterior inferior cerebellar artery[tiab] AND stroke[tiab]) OR (labyrinthine artery[tiab] AND infarct*[tiab]) OR (labyrinthine artery[tiab] AND stroke[tiab])) AND ("Betahistine"[Mesh] OR acuver*[tiab] OR am-125[tiab] OR am-201[tiab] OR am125[tiab] OR am201[tiab] OR antivom*[tiab] OR behistep*[tiab] OR bestin*[tiab] OR betabare*[tiab] OR betabire*[tiab] OR betagen*[tiab] OR betahecon*[tiab] OR betahistin*[tiab] OR beta-histin*[tiab] OR betalune*[tiab] OR betaserc*[tiab] OR betaserk*[tiab] OR fortamid*[tiab] OR histigen*[tiab] OR lectil[tiab] OR marac[tiab] OR marak[tiab] OR meniserc*[tiab] OR microser*[tiab] OR neatin*[tiab] OR pt-9[tiab] OR serc[tiab] OR sinmenier*[tiab] OR vasomotal*[tiab] OR vertiserc*[tiab])
Cinnarizine with or without dimenhydrinate and specific conditions	(vestibular migraine[tiab] OR "Benign Paroxysmal Positional Vertigo"[Mesh] OR BPPV[tiab] OR "Vertebrobasilar Insufficiency"[Mesh] OR vertebrobasilar insufficienc*[tiab] OR vertebro-basilar insufficienc*[tiab] OR vertebrobasilar ischemia[tiab] OR vertebro-basilar ischemia[tiab] OR "Ischemic Attack, Transient"[Mesh] OR transient ischemic attack*[tiab] OR TIA[tiab] OR TIAs[tiab] OR (anterior inferior cerebellar artery[tiab] AND infarct*[tiab]) OR (anterior inferior cerebellar artery[tiab] AND stroke[tiab]) OR (labyrinthine artery[tiab] AND infarct*[tiab]) OR (labyrinthine artery[tiab] AND stroke[tiab])) AND ("Cinnarizine"[Mesh] OR aplactan*[tiab] OR aplexal*[tiab] OR apomitere*[tiab] OR apotomin*[tiab] OR artate*[tiab] OR carecin*[tiab] OR cerebolan*[tiab] OR cerepar*[tiab] OR cibine*[tiab] OR cimarizine*[tiab] OR cinabioquim*[tiab] OR cinaperazine*[tiab] OR cinazyn*[tiab] OR cinnabene*[tiab] OR cinnacet*[tiab] OR cinnaforte*[tiab] OR cinnageron*[tiab] OR cinnarazin*[tiab] OR cinnarizin*[tiab] OR cinarizin*[tiab] OR cinnipirine*[tiab] OR cinniprine*[tiab] OR corathiem*[tiab] OR denapol*[tiab] OR dimitron*[tiab] OR dimitronal*[tiab] OR eglen*[tiab] OR giganten*[tiab] OR glanil*[tiab] OR hilactan*[tiab] OR ixertol*[tiab] OR katoseran*[tiab] OR labyrin[tiab] OR lazeta*[tiab] OR marisan*[tiab] OR md-516*[tiab] OR 516-md[tiab] OR midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r516[tiab] OR roin[tiab] OR sedatromin*[tiab] OR sepan*[tiab] OR siptazin*[tiab] OR spaderizine*[tiab] OR stugeron*[tiab] OR stutgeron*[tiab] OR stutgin*[tiab] OR arlevert*[tiab])
Comparator	No search string
Outcome	“Technology Assessment, Biomedical”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Quality-Adjusted Life Years”[Mesh] OR technology assessment*[tiab] OR economic evaluat*[tiab] OR economic value[tiab] OR cost-benefit*[tiab] OR cost-effectiv*[tiab] OR cost-efficien*[tiab] OR cost-efficac*[tiab] OR cost-minim*[tiab] OR cost-utilit*[tiab] OR cost-consequen*[tiab] OR quality-adjusted life-year*[tiab] OR quality-adjusted lifeyear*[tiab] OR qaly*[tiab]
Limits	No conference abstracts and preprints: NOT (congress[pt] OR preprint[pt])
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

Table 98. Embase.com, additional systematic literature search

Betahistine and specific conditions	('vestibular migraine':ti,ab OR 'vertebrobasilar insufficiency'/exp OR 'vertebrobasilar insufficienc*':ti,ab OR 'vertebro-basilar insufficienc*':ti,ab OR 'vertebrobasilar ischemia':ti,ab OR 'vertebro-basilar ischemia':ti,ab OR 'transient ischemic attack'/exp OR 'transient ischemic attack*':ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ('anterior inferior cerebellar artery':ti,ab AND infarct*:ti,ab) OR ('anterior inferior cerebellar artery':ti,ab AND stroke:ti,ab) OR ('labyrinthine artery':ti,ab AND infarct*:ti,ab) OR ('labyrinthine artery':ti,ab AND stroke:ti,ab)) AND ('betahistine'/exp OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab)
Cinnarizine with or without dimenhydrinate and specific conditions	('vestibular migraine':ti,ab OR 'benign paroxysmal positional vertigo'/exp OR BPPV:ti,ab OR 'vertebrobasilar insufficiency'/exp OR 'vertebrobasilar insufficienc*':ti,ab OR 'vertebro-basilar insufficienc*':ti,ab OR 'vertebrobasilar ischemia':ti,ab OR 'vertebro-basilar ischemia':ti,ab OR 'transient ischemic attack'/exp OR 'transient ischemic attack*':ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ('anterior inferior cerebellar artery':ti,ab AND infarct*:ti,ab) OR ('anterior inferior cerebellar artery':ti,ab AND stroke:ti,ab) OR ('labyrinthine artery':ti,ab AND infarct*:ti,ab) OR ('labyrinthine artery':ti,ab AND stroke:ti,ab)) AND ('cinnarizine'/exp OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516-md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r51:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab)
Comparator	No search string
Outcome	'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ti,ab
Limits	No conference abstracts and preprints/select other publication types: AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

Table 99. Cochrane Library, additional systematic literature search

Betahistine and specific conditions	("vestibular migraine":ti,ab OR [mh "Vertebrobasilar Insufficiency"] OR (vertebrobasilar NEXT insufficienc*):ti,ab OR (vertebro-basilar NEXT insufficienc*):ti,ab OR (vertebrobasilar NEXT ischemia):ti,ab OR (vertebro-basilar NEXT ischemia):ti,ab OR [mh "Ischemic Attack, Transient"] OR ("transient ischemic" NEXT attack*):ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ("anterior inferior cerebellar artery":ti,ab AND infarct*:ti,ab) OR ("anterior inferior cerebellar artery":ti,ab AND stroke:ti,ab) OR ("labyrinthine artery":ti,ab AND infarct*:ti,ab) OR ("labyrinthine artery":ti,ab AND stroke:ti,ab)) AND ([mh Betahistine] OR acuver*:ti,ab OR am-125:ti,ab OR am-201:ti,ab OR am125:ti,ab OR am201:ti,ab OR antivom*:ti,ab OR behistep*:ti,ab OR bestin*:ti,ab OR betabare*:ti,ab OR betabire*:ti,ab OR betagen*:ti,ab OR betahecon*:ti,ab OR betahistin*:ti,ab OR beta-histin*:ti,ab OR betalune*:ti,ab OR betaserc*:ti,ab OR betaserk*:ti,ab OR fortamid*:ti,ab OR histigen*:ti,ab OR lectil:ti,ab OR marac:ti,ab OR marak:ti,ab OR meniserc*:ti,ab OR microser*:ti,ab OR neatin*:ti,ab OR pt-9:ti,ab OR serc:ti,ab OR sinmenier*:ti,ab OR vasomotal*:ti,ab OR vertiserc*:ti,ab)
Cinnarizine with or without dimenhydrinate and specific conditions	("vestibular migraine":ti,ab OR [mh "Benign Paroxysmal Positional Vertigo"] OR BPPV:ti,ab OR [mh " Vertebrobasilar Insufficiency"] OR (vertebrobasilar NEXT insufficienc*):ti,ab OR (vertebro-basilar NEXT insufficienc*):ti,ab OR (vertebrobasilar NEXT ischemia):ti,ab OR (vertebro-basilar NEXT ischemia):ti,ab OR [mh "Ischemic Attack, Transient"] OR ("transient ischemic" NEXT attack*):ti,ab OR TIA:ti,ab OR TIAs:ti,ab OR ("anterior inferior cerebellar artery":ti,ab AND infarct*:ti,ab) OR ("anterior inferior cerebellar artery":ti,ab AND stroke:ti,ab) OR ("labyrinthine artery":ti,ab AND infarct*:ti,ab) OR ("labyrinthine artery":ti,ab AND stroke:ti,ab)) AND ([mh Cinnarizine] OR aplactan*:ti,ab OR aplexal*:ti,ab OR apomitere*:ti,ab OR apotomin*:ti,ab OR artate*:ti,ab OR carecin*:ti,ab OR cerebolan*:ti,ab OR cerepar*:ti,ab OR cibine*:ti,ab OR cimarizine*:ti,ab OR cinabioquim*:ti,ab OR cinaperazine*:ti,ab OR cinazyn*:ti,ab OR cinnabene*:ti,ab OR cinnacet*:ti,ab OR cinnaforte*:ti,ab OR cinnageron*:ti,ab OR cinnarazin*:ti,ab OR cinnarizin*:ti,ab OR cinarizin*:ti,ab OR cinnipirine*:ti,ab OR cinniprine*:ti,ab OR corathiem*:ti,ab OR denapol*:ti,ab OR dimitron*:ti,ab OR dimitronal*:ti,ab OR eglen*:ti,ab OR giganten*:ti,ab OR glanil*:ti,ab OR hilactan*:ti,ab OR ixertol*:ti,ab OR katoseran*:ti,ab OR labyrin:ti,ab OR lazeta*:ti,ab OR marisan*:ti,ab OR md-516*:ti,ab OR 516md:ti,ab OR midronal*:ti,ab OR mitronal*:ti,ab OR olamin*:ti,ab OR processine*:ti,ab OR r-1575:ti,ab OR r-516:ti,ab OR r1575:ti,ab OR r51:ti,ab OR roin:ti,ab OR sedatromin*:ti,ab OR sepan*:ti,ab OR siptazin*:ti,ab OR spaderizine*:ti,ab OR stugeron*:ti,ab OR stutgeron*:ti,ab OR stutgin*:ti,ab OR arlevert*:ti,ab)
Comparator	No search string
Outcome	[mh "Technology Assessment, Biomedical"] OR [mh "Cost-Benefit Analysis"] OR [mh "Quality-Adjusted Life Years"] OR technology assessment*:ti,ab OR economic evaluat*:ti,ab OR economic value:ti,ab OR cost-benefit*:ti,ab OR cost-effectiv*:ti,ab OR cost-efficien*:ti,ab OR cost-efficac*:ti,ab OR cost-minim*:ti,ab OR cost-utilit*:ti,ab OR cost-consequen*:ti,ab OR quality-adjusted life-year*:ti,ab OR quality-adjusted lifeyear*:ti,ab OR qaly*:ti,ab
Limits	No conference abstracts and preprints: NOT (congress:pt OR preprint:pt)
	Substract the output from the primary systematic literature search, to avoid screening duplicate records
Search date	29 January 2024

Table 100. Tufts Medical Centre Cost-Effectiveness Analysis Registry and international HTA database, additional systematic literature search

Population	"vestibular migraine" OR "Vertebrobasilar Insufficiency" OR "Transient Ischemic Attack" OR TIA OR ("anterior inferior cerebellar artery" AND infarct*) OR ("anterior inferior cerebellar artery" AND stroke) OR ("labyrinthine artery" AND infarct*) OR ("labyrinthine artery" AND stroke)
Intervention	"vestibular migraine" OR "Benign Paroxysmal Positional Vertigo" OR BPPV OR "Vertebrobasilar Insufficiency" OR "Transient Ischemic Attack OR TIA OR ("anterior inferior cerebellar artery" AND infarct) OR ("anterior inferior cerebellar artery" AND stroke) OR ("labyrinthine artery" AND infarct) OR ("labyrinthine artery" AND stroke)
Comparator	No search string
Outcome	No search string
Limits	Language: English, French, German, Italian
Search date	6 February 2024

G. Excludes during full-text selection economic systematic review

Table 101. Excluded studies found with the economic systematic literature search for RCTs

Reference	Reason for exclusion
Wang Y, Wu M, Cheng P, Pei S, Liu Y, Liu Y. Analysis of cost and effectiveness of treatment in benign paroxysmal positional vertigo. Chin Med J. 2019;132(3):342-345. doi:10.1097/CM9.0000000000000063	Irrelevant publication type (editorial)
National Guideline Centre (UK). Evidence review for betahistine: Tinnitus: assessment and management. National Institute for Health and Care Excellence (NICE). 2020.	Outcome out of scope
Hesse G, Rienhoff NK, Nelting M, Brehmer D. Medicine costs in patients with chronic complex tinnitus. HNO. 1999;47(7):658-60	Comparator out of scope