Health Technology Assessment (HTA)

HTA Protocol

Title	Treatment with betahistine or cinnarizine with or without dimenhydrinate for adult patients with Ménière's disease/syndrome and patients experiencing symptoms of vestibular vertigo and/or tinnitus
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Executive summary

Ménière's disease is a disorder of the inner ear that can cause various symptoms, including vertigo (a sensation of self-motion), tinnitus (a persistent ringing or other noise in the ear), hearing loss and aural fullness (a feeling of pressure deep inside the ear). In Switzerland, betahistine (an analogue of histamine) and cinnarizine (a selective calcium channel blocker and an antihistamine) are being 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 being reimbursed for the symptomatic treatment of transient vertigo. Within the context of the Federal Office of Public Health (FOPH) Health Technology Assessment (HTA) Program, the evidence for these coverage decisions is to be re-evaluated. The HTA report following this HTA protocol will present the best available evidence regarding the application of 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. 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.

For the clinical evaluation, a systematic literature search of the PubMed (MEDLINE), Embase.com and Cochrane Library databases will be conducted adhering to international methodological standards. A stepwise systematic literature search approach will be implemented: first a search for randomised controlled trials (RCTs) and, in case less than 2 RCTs are found for the primary efficacy and safety outcomes, an additional search for comparative non-randomised studies. Search strings will be compiled for the population (Ménière's disease or symptoms of vertigo and/or tinnitus) and the intervention (betahistine or cinnarizine with or without dimenhydrinate). Studies will be selected by applying pre-specified exclusion criteria during the selection process. Included studies will be critically appraised and extracted. The options for clinically relevant data merging/stratification and calculation of pooled estimates by meta-analysis will be explored after data-extraction.

For the economic evaluation, systematic literature searches of the previously mentioned databases and economic databases (the Tufts Medical Centre Cost-Effectiveness Analysis Registry and the International HTA Database) will identify existing economic studies that are applicable to the policy question. Search strings will be compiled comparable to the search strings used within the clinical evaluation, with economic outcomes. Studies will be selected by applying pre-specified exclusion criteria and the included studies will be critically appraised and extracted.

In case the outcomes of the clinical evaluation show an added benefit of betahistine and/or cinnarizine with or without dimenhydrinate, an economic evaluation will be conducted. Results from the systematic review on economic evaluations will be used to construct a health economic model to evaluate the cost-effectiveness of betahistine and cinnarizine with or without dimenhydrinate. The analysis will utilise up-to-date Swiss-specific cost and clinical inputs that are most applicable to the Swiss context. Finally, a budget impact analysis will be conducted.

For the evaluation of the ethical, legal, social and organisational domains, relevant issues will be identified from the studies included in the clinical and economic evaluation. In addition, targeted non-systematic searches will be conducted to identify grey literature related to these domains; key issues will be summarised narratively.

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Abbreviations and acronyms

AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery
CEA	Cost-effectiveness analysis
CHEERS	Consolidated health Economic Evaluation Reporting Standards
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
mg	Milligram
ml	Millilitre
PICO	Population, intervention, comparator and outcome
PRISMA	Preferred Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RoB 2	Revised Cochrane Risk of Bias tool for randomised trials
ROBINS-I	Risk of Bias in Non-randomised Studies - of Interventions
USA	United States of America

Objective of the HTA Protocol

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

1 Policy question

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. The HTA report following this HTA protocol will present the best available evidence regarding the application of 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. 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 persistent ringing or other noise in the ear. 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 Barany 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 and vestibular neuronitis are considered to be the most common (peripheral) causes of vestibular vertigo.[15] 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,[19] patients with Ménière's disease often have a reduced quality of life (QoL).[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 attacks and improve QoL.[16] Typically, diuretics (also known as water pills) and betahistine are recommended as first-line treatments. Intratympanic corticosteroids or gentamicin, and surgical treatments (ranging from conservative to destructive) can be considered in subsequent treatment lines.[12,13]

3 Technology description

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 protocol, 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.

Table 1. Indications

Medication	Indications[2]	Mode of application[2]	Dosing[2]
Betahistine	• Vertigo caused by problems with blood flow to the inner ear • Ménière's syndrome and Ménière-like syndromes (vertigo, tinnitus, hearing loss)	• Tablets • Oral drops	• Daily dose 24 mg (8 mg 3x daily) or 48 mg (16 mg 3x daily *or* 24 mg 2x daily) • The usual dose is 3x 1-2 ml (24 - 48 mg) or 2x 3 ml (48 mg) daily
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	• Capsules • Oral drops	• 1 capsule of 75 mg once a day • 8 drops (24 mg) 3 times a day
Cinnarizine with dimenhydrinate	Symptomatic treatment of transient vertigo (up to a maximum of 4 weeks)	• Tablets	• 1 tablet 3 times a day (1 tablet contains 20 mg cinnarizinum and 40 mg dimenhydrinatum)

Abbreviations
mg = milligram, ml = millilitre.

3.1 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]

3.2 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]

3.3 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]

4 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] • Cinnarizine[a] • Cinnarizine with dimenhydrinate[a,b]
Comparator	• Placebo[a] • No treatment[a]
Outcome	Efficacy and effectiveness[c] Primary outcomes: • Vertigo[d] • Tinnitus • Hearing Secondary outcomes: • Disease-specific HRQoL • HRQoL Safety Primary outcome: • Serious adverse events[e] Secondary outcome: • Other adverse events[f] Economics • Incremental/total costs, life years and QALYs • ICER • Budget impact analysis

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 = Cinnarizine with dimenhydrinate is licensed only for the symptomatic treatment of transient vertigo; this intervention is therefore not relevant for all subpopulations.
c = 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.
d = The number (e.g. number of attacks per month), severity and duration of attacks will be assessed.
e = 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.
f = 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 key questions

For the evaluation of the technology (***Chapter 3***), the following key questions covering central HTA domains, as designated by the European Network for Health Technology Assessment Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, ethical, legal, social and organisational aspects), are addressed:

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

6 Methodology

The general methodology for the HTA will consist of one systematic review for the clinical evaluation (***Chapter 6.1***), one systematic review for the economic evaluation (***Chapter 0***) and non-systematic reviews for the evaluation of the ethical, legal, social and organisational domains of the HTA (***Chapter 6.3***). The proposed methodology for the health economic and budget-impact modelling is outlined in ***Chapter 6.2.3*** and ***Chapter 6.2.4***.

6.1 Clinical evaluation

A systematic review is a method to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question.[21] The systematic review methodology described in this protocol is developed in line with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3)[21] and the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22]

6.1.1 Databases and search strategy

A stepwise systematic literature search approach will be implemented: (1) a systematic literature search for randomised controlled trials (RCTs); and (2) in case overall less than 2 RCTs are found for the primary efficacy and safety outcomes, an additional systematic literature search for comparative non-randomised studies. Systematic literature searches will be 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 will be conducted on the websites of ClinicalTrials.gov

(https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu).

The search strategy is developed with an information specialist based on the PICO reported in ***Chapter 4***. As quality control the search strategy is checked by a second researcher. Search strings are 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 is added to exclude conference abstracts and preprints. Studies will be selected by applying pre-specified exclusion criteria during the selection process (***Table 3***). Swiss clinical experts will be consulted in order to check whether studies identified on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fall within the scope of the licensed indications of the interventions. An additional systematic literature search for relevant indications may be performed.

The syntax of the search strategy is composed for one medical database, PubMed (MEDLINE), and customised to the other databases. The details of the search strategies are outlined in ***Appendix 9.1***.

Electronic records of the articles retrieved by the searches will be stored by using Endnote reference manager software (Clarivate Analytics, United States of America [USA]). This Endnote file will be uploaded in Rayyan software (Rayyan Systems Inc., USA) for the selection of the articles.[23] Duplicate records will be deleted, and this number will be registered in the PRISMA flow diagram.

6.1.2 Study selection

Relevant articles will be selected in duplicate by a systematic approach by 2 independent researchers. Firstly, the major topics of the articles will be assessed on relevancy to the objectives by the title and abstract. Articles that seem to contain relevant data for the objectives will be selected for full-text screening. Articles without relevancy to the objectives will be excluded, without documenting the reason for exclusion. If the 2 researchers disagree on the relevance of an article, this will be discussed. If the differences remain after discussion, the article will be assessed in full text. Secondly, the articles will be assessed in full text based on the pre-specified eligibility criteria. Articles will be included in the systematic review if they fulfil the inclusion criteria; the remaining articles will be excluded and the primary reason for exclusion will be listed. Any differences between the 2 researchers will be resolved by discussion, if needed a third researcher will be consulted.

The search results will be screened against the pre-specified eligibility criteria, based on elements of the article, study design and PICO (***Chapter 4***). If relevant additional criteria emerge during the study selection, this table will be complemented in close collaboration with the FOPH. To avoid steering the

study selection, the FOPH will be blinded for the study details and results during this process. The final list of applied inclusion and exclusion criteria will be presented in the HTA report.

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

Reference lists of relevant systematic reviews to the research question identified during the title and abstract screening will be checked for potentially relevant additional references of primary studies. Narrative reviews will be excluded directly and not be checked for references. The systematic review itself will be excluded after the reference check, with a documented reason for exclusion in the PRISMA flow diagram. In addition, the supplementary search technique backward citation chasing will be applied, i.e. by finding other studies cited within the included articles. All the additionally found primary studies will be assessed based on the pre-specified eligibility criteria.

Table 3. Inclusion and exclusion criteria for clinical evaluation studies

	Inclusion criteria	Exclusion criteria
Publication year	All	None
Language of publication	English, French, German and 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 (i.e. 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 (to be decided during the project)[c] • Adult patients with other peripheral or central vestibular disorders experiencing symptoms of tinnitus (to be decided during the project)[c]	• Animal studies • Patients aged <18 years • Patients who had already undergone destructive medical or surgical treatment (e.g. intratympanic gentamicin, 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 reimbursement because of other pathomechanisms (to be decided during the project)[c]
Intervention	• Betahistine[d] • Cinnarizine[d] • Cinnarizine with dimenhydrinate[d]	Other interventions
Comparator	• Placebo[d] • No treatment[d]	• Other comparators • No comparator
Outcome	• Vertigo • Tinnitus • Hearing • Disease-specific HRQoL • HRQoL • Serious adverse events[e]	• Studies with duplicate data (study with the largest sample size or most extended follow-up will be included for data extraction of the results[g]) • Other outcomes

	• Other adverse events[f]	
Study quality		• Inadequate data (e.g. missing relevant data or unexplained important errors in patient flow)[h] • Comparative non-randomised studies not adjusting for main confounders

Abbreviations
HRQoL = health-related quality of life, RCTs = randomised controlled trials.
Notes
a = These studies will only be included in case less than 2 RCTs are 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 will be included.
c = Swiss clinical experts will be consulted in order to check whether studies identified on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fall within the scope of the licensed indications of the interventions. Indications which are out of scope because of other pathomechanisms will be excluded during the full-text selection with a documented reason for exclusion in the PRISMA flow diagram.
d = The interventions could also be evaluated together with co-interventions as long as these co-interventions are identical with those in the comparator arm.
e = 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.
f = 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.
g = If applicable, unique results from interim studies will 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.
h = If applicable, a specific exclusion criterion will be formulated to be transparent on the details of the inadequate data and this will be reported in the HTA report.

6.1.3 Data extraction

Relevant data from the included studies found in the medical journal databases will be independently extracted by one researcher into a standardised data-extraction spreadsheet in Microsoft Excel. The data-extraction spreadsheet will be fully reviewed by a second researcher, differences will be resolved by discussion and in case of discrepancy a third researcher will be consulted to reach consensus. This spreadsheet will include:

- 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 co-medication);
- 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 will need to be considered not identifiable from other extracted data).

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

- 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.

6.1.4 Analysis of study quality

Risk of bias of included studies

The included studies will be critically appraised by one researcher using different tools depending on the study design. The critical appraisal will be fully reviewed by a second researcher, differences will be resolved by discussion and in case of discrepancy a third researcher will be consulted to reach consensus. The quality of RCTs will be assessed with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2).[21,24] RoB 2 is a results-based tool which assesses the risk of bias in an RCT for specific outcomes instead of assessing the risk of bias for the RCT as whole. If applicable, the comparative non-randomised studies will be assessed with the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool.[25] The risk of bias assessments will be visualised in plots with the web application Robvis.[26]

Overall certainty of the evidence

The overall certainty of the evidence on outcome level will be appraised by one researcher using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[21,27] The GRADE assessment will be fully reviewed by a second researcher, differences will be resolved by discussion and in case of discrepancy a third researcher will be consulted to reach consensus. The 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 involves appraisal of 5 domains: (1) risk of bias (i.e. study limitations; as assessed with the RoB 2 tool and ROBINS-I 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 (i.e. random error) and (5) the risk of publication bias. If applicable, 3 domains can upgrade the certainty of evidence of comparative non-randomised studies (i.e. a large effect, a dose-response gradient or plausible residual opposing confounding). Based on the assessments for each domain, the overall evaluation of the certainty of the evidence per outcome can be classified as high, moderate, low or very low. The overall certainty of the evidence will be summarised in a GRADE summary of findings table, together with key information concerning the magnitudes of relative and absolute effects of the intervention and the amount of available evidence.[21,27] GRADEpro GDT software (Evidence Prime Inc., Canada) will be used to construct the summary of findings table for up to a maximum of 7 patient-important outcomes (i.e. the primary and secondary efficacy and effectiveness outcomes and the primary safety outcomes).[28]

6.1.5 Data analysis and synthesis of efficacy, effectiveness and safety outcomes

The extracted data of the included studies in the Microsoft Excel spreadsheet will be summarised in study characteristics tables, risk of bias figures, summary tables and a GRADE summary of findings table. When possible, forest plots will be created to visualise the results. These tables and figures will be fully reviewed by a second researcher, differences will be resolved by discussion and in case of discrepancy a third researcher will be consulted to reach consensus.

Based on the heterogeneity of the study characteristics and data reported in the included studies, the options for clinically relevant data merging/stratification will be explored and, if necessary, discussed with a clinical expert. The clinical expert will be blinded for the study results during this process. Subgroups will be considered for patients with (1) Ménière's disease (definite and/or probable), (2) patients with symptoms of vestibular vertigo and (3) patients with symptoms of tinnitus. If feasible, further subgroups will be defined, for example distinguishing Ménière's disease from Ménière's syndrome, peripheral from central vestibular vertigo, and patients with different underlying causes of vestibular vertigo. The feasibility depends on the level of detail about the population within the identified studies. The details of the applied data merging/stratification will be reported in the methodology section of the HTA report.

Pooled estimates will be calculated by meta-analysis for outcomes reported by at least 2 studies; if the outcome measures can be combined. If applicable, separate pooled estimates will be calculated for the outcome data of RCTs (providing efficacy data) and the comparative non-randomised studies (providing effectiveness data). Considering the expected heterogeneity in the data, a random-effects model (i.e. DerSimonian and Laird) will be used for the analyses.[21] Heterogeneity will be assessed graphically with forest plots and statistically using the Chi^2 test, the I^2 statistic and prediction intervals. The analyses will be conducted with the Comprehensive Meta-Analysis software (Biostat, USA). For outcomes reported in a minimum of 10 studies, the publication bias will be assessed using tests for funnel plot asymmetry. The results of the clinical trial registry search will be used for a narrative description of publication bias.

Outcomes for which it is not possible to calculate pooled estimates will be analysed narratively and presented in summary tables. A range of relative effects from the studies or direction of the effect will be presented.

6.2 Economic evaluation

6.2.1 Databases and search strategy

6.2.1.1 Search strategy

The cost-effectiveness systematic literature search follows the principles of the systematic literature search for the clinical evaluation outlined in ***Chapter 6.1***. PubMed (MEDLINE), Cochrane library and Embase.com databases will be searched for peer-reviewed scientific literature. In addition, economic databases (the Tufts Medical Centre Cost-Effectiveness Analysis [CEA] Registry and the International HTA Database) will be searched. The searches are built using the PICO reported in ***Chapter 4***. In PubMed (MEDLINE), Cochrane library and Embase.com, the search terms of the efficacy, effectiveness and safety literature search will be combined with cost-effectiveness search terms. The details of the search strategy are presented in ***Appendix 9.2***.

6.2.1.2 Selection procedure

All articles retrieved from PubMed (MEDLINE), Cochrane library, Embase.com, CEA Registry, International HTA Database and relevant references will be reviewed in duplicate by 2 independent researchers in a similar manner to the systematic approach described in ***Chapter 6.1.2***, including firstly screening title and abstract and subsequently full-text screening. In the first step, the major topics of the articles will be assessed based on relevancy and articles that seem to contain relevant data for the HTA objectives will be selected for the full-text screening. Subsequently, the articles screened in full-text are assessed for inclusion based on pre-specified eligibility criteria defined in the HTA protocol (***Table 4***). Like with the clinical evaluation eligibility criteria, if any relevant additional criteria emerge during the study selection, this table will be complemented in close collaboration with the FOPH, and the same blinding approach will be applied to avoid steering the study selection. The final list of applied inclusion and exclusion criteria will be presented in the HTA report.

The titles and abstracts retrieved by the systematic literature searches will be screened in duplicate by 2 independent researchers. If the 2 researchers disagree on the relevance of an article, this will be discussed. If the differences remain after discussion, the article will be assessed in full text. Also the screening of full-text articles will be done in duplicate by 2 independent researchers. Again any differences will be resolved by discussion, and if needed a third researcher will be consulted.

The process of selection and inclusion and exclusion of articles will be recorded with Rayyan software (Rayyan Systems Inc., USA) and in Endnote. This method will provide transparency regarding all selection steps and assures reproducibility. The selection procedure applied during the full-text screening phase will be reported in a PRISMA flow diagram and primary reasons for exclusion per excluded article will be listed in a table, like in the clinical evaluation approach.

6.2.1.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria which will be applied during the selection processes are listed in ***Table 4***.

Table 4. 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 (to be decided during the project)[b] • Adult patients with other peripheral or central vestibular disorders experiencing symptoms of tinnitus (to be decided during the project)[b]	• Animal studies • Patients aged <18 years • Patients who had already undergone destructive medical or surgical treatment (e.g. intratympanic gentamicin, 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 reimbursement because of other pathomechanisms (to be decided during the project)[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 will be included.

b = Swiss clinical experts will be consulted in order to check whether studies identified on specific other peripheral or central vestibular disorders with symptoms of vestibular vertigo and/or tinnitus fall within the scope of the licensed indications of the interventions. Indications which are out of scope because of other pathomechanisms will be excluded during the full-text selection with a documented reason for exclusion in the PRISMA flow diagram.
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 will be included and interim studies might be used as additional input on the study methodology.

6.2.2 Data extraction, analysis and synthesis

6.2.2.1 Data extraction

The following relevant data from the included articles found in the peer-reviewed literature will be 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 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 will be fully checked with the original articles by a second researcher.

6.2.2.2 Critical appraisal

The identified studies from the systematic literature search for cost-effectiveness will be subjected to a critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[29] as recommended by current guidelines.[30] The CHEERS is a 24-item checklist with clear questions about the economic evaluation that gives insight into the general quality of the study.

6.2.2.3 Data synthesis

Data synthesis will be done using descriptive comparisons of the study question, methods and results. Summary tables will be included which will present key information described in the data extraction ***Chapter 6.2.2.1***. The incremental cost-effectiveness ratios (ICERs) will be presented and the reliability (internal validity) and relevance (generalisability) of the estimates will be explored applying the appraisal

tools described in ***Chapter 6.2.2.2***. The analytical approaches used in the studies will be compared and their robustness will be discussed.

6.2.3 Economic model protocol

In case the outcomes of the clinical evaluation show an added benefit of betahistine and/or cinnarizine with or without dimenhydrinate, an economic evaluation will be conducted. Whether an economic evaluation is deemed useful can vary between subgroups. The following section describes the proposed approach for the economic evaluation, if applicable.

6.2.3.1 Target population

The target population for the economic evaluation consists of adult patients with Ménière's disease, or adult patients experiencing symptoms of vestibular vertigo and/or tinnitus.

6.2.3.2 Setting and location

The analysis will be performed for the Swiss healthcare setting. This means that where possible and relevant input parameters will be based on data from Switzerland (e.g. Swiss sources for healthcare costs).

6.2.3.3 Study perspective

The analysis will be performed from a healthcare payer perspective. This means that only the costs within the healthcare sector will be included. Societal costs, such as informal care and productivity costs, will not be included.

6.2.3.4 Interventions

The interventions of interest are betahistine and cinnarizine with or without dimenhydrinate. These are all relevant for the target population, except cinnarizine with dimenhydrinate which is only reimbursed for the symptomatic treatment of transient vertigo.

6.2.3.5 Comparators

Betahistine and cinnarizine with or without dimenhydrinate will be compared to no treatment.

6.2.3.6 Time horizon

The preferred time horizon of the base-case analysis is lifetime. The feasibility of implementing a lifetime horizon will depend on the availability of data. Shorter time horizons will be considered in scenario analyses, if relevant.

6.2.3.7 Discount rate

In the base-case analysis, costs and effects will be discounted at 3.0%. In scenario analyses, the impact of not discounting or using a discount rate of 5.0% will be explored.

6.2.3.8 Health outcomes

Health outcomes will be reported in life years and QALYs.

6.2.3.9 Currency, price data and conversion

Costs from the Swiss Federal Statistical Office will be reported in CHF in 2022 values. When necessary, prices will be adjusted to 2022 price levels using inflation rates, which will be accessed from the Organization for Economic Co-operation and Development website (https://data.oecd.org).

6.2.3.10 Model structure

The structure of the health economic model will reflect the clinical evidence and can be informed by previously published models evaluating the cost-effectiveness of betahistine or cinnarizine with or without dimenhydrinate compared to no treatment. Within the model, different data sources will be combined to link clinical outcomes to outcomes that are relevant from a health economic perspective, such as life years and QALYs. Furthermore, the model will be used to extend available information beyond trial durations.

The model will be programmed in statistical programming language R [31] based on the framework developed by the Decision Analysis in R for Technologies in Health workgroup [32–34].

6.2.3.11 Input parameters

The model input parameters on clinical outcomes, adverse events and HRQoL will be informed by the results of the systematic review on the efficacy, effectiveness and safety of betahistine and cinnarizine with or without dimenhydrinate.

All costs within the healthcare sector will be considered, such as drug costs, disease monitoring costs and (if modelled) the costs of adverse events. Where possible, Swiss resource use will be used. If not available, international data on resource use will be used instead, multiplied with Swiss unit costs as supplied by the FOPH. If resource use data is not available, international cost estimates will be used.

If no Swiss-specific data on costs, resource use and utilities are identified in the systematic reviews on the efficacy, effectiveness, safety and cost-effectiveness described in this report, additional pragmatic searches will be performed. Clinical expert opinion will be used whenever necessary data is unavailable from the literature.

6.2.3.12 Analytical methods

6.2.3.12.1 Base-case analysis

The base-case analysis will consider the entire target population of patients with Ménière's disease, or patients with symptoms of vestibular vertigo and/or tinnitus, and will be conducted as described in the previous sections. If the available evidence does not allow for an evaluation of the interventions across the entire target population, only subgroup analyses (as defined below) will be conducted.

6.2.3.12.2 Subgroup and scenario analyses

Subgroup analyses will consider patients with (1) Ménière's disease (definite and/or probable), (2) symptoms of vestibular vertigo and (3) symptoms of tinnitus. If feasible, further subgroups will be defined, for example distinguishing Ménière's disease from Ménière's syndrome, peripheral from central vestibular vertigo, and patients with different underlying causes of vestibular vertigo. The feasibility depends on the level of detail about the population within the identified studies. The details of the applied data merging/stratification will be reported in the methodology section of the HTA report.

Structural uncertainty is tested in scenario analyses. If feasible given the available evidence, scenario-analyses will be conducted with either placebo-controlled studies or studies comparing one of the interventions to no treatment.

6.2.3.12.3 One-way sensitivity analyses

Parameter uncertainty is first tested using one-way sensitivity analyses; model parameters are systematically and independently varied over a plausible range (e.g. using the 95% confidence interval or a 20% increase/decrease of the parameter value used in the base-case). The ICER is recorded at the upper and lower limits to produce tornado diagrams.

6.2.3.12.4 Probabilistic sensitivity analyses

Joint parameter uncertainty is explored through probabilistic sensitivity analysis where all parameters, to which probability distributions are assigned, are varied jointly. Monte Carlo simulations will be performed, and the results will be recorded. Results will be plotted on the cost-effectiveness plane. From these results, a cost-effectiveness acceptability curve will be estimated.

6.2.4 Budget impact analysis

In addition to the cost-effectiveness model, a budget impact model will be developed to estimate the projected population-level overall costs of betahistine and cinnarizine with or without dimenhydrinate in adult patients with Ménière's disease or symptoms of vestibular vertigo and/or tinnitus from the

healthcare payer perspective. The budget impact model will be built as an extension to the cost-effectiveness model, described above. Hence, the core model characteristics for the budget impact model will be dependent on the cost-effectiveness model. In case no economic evaluation is carried because of a lack of evidence or in case the evidence does not show a positive effect, the budget impact analysis will remain relevant and will still be carried out. The budget impact model will then be informed using the methodology described above.

The time horizon will be restricted to 5 years for the period 2024-2028. For the budget impact model, data is required about the current use of betahistine and cinnarizine with or without dimenhydrinate in patients with Ménière's disease or symptoms of vestibular vertigo and/or tinnitus in Switzerland. Data on current use will be provided by the FOPH if such data is available. If this data is not available, assumptions will be made based on data from other comparable countries and/or expert opinion. Similar to the economic evaluation, subgroup analyses will consider patients with (1) Ménière's disease (definite and/or probable), (2) symptoms of vestibular vertigo and (3) symptoms of tinnitus. Uncertainty will be addressed with scenario analyses.

6.3 Evaluation of the ethical, legal, social and organisational domains

The full texts of studies identified for the evaluation of the ethical, legal, social and organisational domains encountered during the systematic reviews on the efficacy, effectiveness, safety and cost-effectiveness will be reviewed. In addition, grey literature on these HTA domains will be searched for on relevant websites, such as the websites of the AAO-HNS and the Bárány Society, and the websites of patient organisations (e.g. www.menieres.org.uk and www.vestibular.org).

7 Summary and outlook

7.1 Summary

In Switzerland, betahistine and cinnarizine are being reimbursed for patients experiencing symptoms of vertigo, tinnitus and hearing loss caused by Ménière's disease or other disorders. Furthermore, cinnarizine with dimenhydrinate is being reimbursed for the symptomatic treatment of transient vertigo. The policy question of this HTA is whether the use of betahistine and cinnarizine with or without dimenhydrinate compared to no treatment meet the effectiveness, appropriateness and economic efficiency criteria for adult patients with Ménière's disease or adult patients with other peripheral or central vestibular disorders experiencing symptoms of vestibular vertigo and/or tinnitus. In this HTA protocol, the HTA key questions and PICO are being described, as well as the methodology to conduct the evaluation.

The methodology consists of a systematic review on the clinical effectiveness and cost-effectiveness of betahistine and cinnarizine with or without dimenhydrinate. In case the outcomes of the clinical evaluation show an added benefit of betahistine and/or cinnarizine with or without dimenhydrinate, an economic evaluation will be conducted. Additionally, a budget impact analysis will be carried out.

The target population is relatively broad and heterogeneous but is being defined in line with the licensed indications of betahistine and cinnarizine with or without dimenhydrinate. Although some subpopulations have been defined within this protocol, additional subpopulations can be specified during the conduct of the HTA, if needed.

7.2 Outlook

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

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9 Appendices

9.1 Search strategy for clinical evaluation systematic literature search

PubMed (MEDLINE)

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 516-md[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 midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r51[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])

Embase.com

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 516-md: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 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)

Cochrane Library

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 516md: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 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)

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

9.2 Search strategy for economic evaluation systematic literature search

PubMed (MEDLINE)

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 516-md[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 midronal*[tiab] OR mitronal*[tiab] OR olamin*[tiab] OR processine*[tiab] OR r-1575[tiab] OR r-516[tiab] OR r1575[tiab] OR r51[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])

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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 516-md: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 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)

Cochrane Library

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 516md: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 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)

Tufts Medical Centre Cost-Effectiveness Analysis Registry and International HTA Database

Population	meniere OR vertigo OR tinnitus
Intervention	betahistine OR cinnarizine
Comparator	No search string
Outcome	No search string