Consolidated stakeholder feedback version 2

HTA protocol

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

Stakeholders (SH; in alphabetical order) that have provided comments:

1	Helsana Versicherungen AG
2	Mylan Pharma GmbH
3	Santésuisse
4	Schweizerische Neurologische Gesellschaft (SNG)
5	Schweizerische ORL-Gesellschaft (SGORL)
6	Zambon Schweiz AG

SH	SH comment	Reply authors / BAG & implemented changes
1	Gemäss der aktuellen deutschen S2K-Leitline 2021 Vestibuläre Funktionsstörungen kann bzgl. M.Meniere keine eindeutige Empfehlung für oder gegen die Therapie mit Betahistin gegeben werden. Für die Therapie mit 3x25mg Cinnarizin fehle derzeit (01/2020) die notwendige Evidenz für eine Leitlinienempfehlung. Sollte sich dies im HTA-Bericht bestätigen, stellt sich die Frage nach Therapiealternativen und wie man mit deren Vergütung umgeht/umgehen will (Transtympanale medikamentöse Therapie mit Gentamycin/Cortison, operative Therapie), respektive ,ob diese ebenfalls im HTA-Bericht zu analysieren wären. Translation: According to the current German S2K guideline 2021 Vestibular dysfunction, no clear recommendation for or against therapy with betahistine can be given with regard to Meniere's disease. There is currently a lack of evidence necessary for a guideline recommendation for therapy with 3x25mg cinnarizine (01/2020). If this is confirmed in the HTA report, the question arises about treatment alternatives and how one deals/wants to deal with their reimbursement (transtympanic drug therapy	This is beyond the scope of the current HTA. No change needed.

	with gentamycin/cortisone, surgical therapy), or whether these should also be analyzed in the HTA report .	
2	Unser Erstaunen liegt darin, dass die Fragestellungen im Rahmen der Leistungsdefinitionsarbeiten des BAG durchgeführt werden. Für Kliniker und Patienten mag es durchaus interessant sein, Betaserc - wie jedes andere Arzneimittel auch - in einer umfassenden Review näher zu beleuchten. Aus OKP-Sicht erscheint das HTA aber obsolet, denn die wesentlichen Erkenntnisse im Hinblick auf eine Vergütungspflicht können in aller Kürze erhoben werden. So würde etwa ein Blick in die Swissmedic-Zulassung verbunden mit einer Evaluation jüngster Studien (z.B. Christine Adrion et al., "Efficacy..." in BMJ 2016;352:h6816) hinreichend Auskunft über die WZW-Konformität von Betaserc geben. Das Resultat dieses HTA ist daher ex ante bereits in einem Grade voraussehbar, der die HTA-Durchführung als unnötiger Ressourceneinsatz erkennen lässt. Betaserc ist ein zugelassenes Arzneimittel, also wirksam, sicher und von guter Qualität. Seine Wirkung und sein Wirkungsausmass mögen im HTA-Ergebnis weiteren Erforschungsbedarf erkennen lassen. Aber die aktuelle Datenlage offenbart bereits ohne HTA, dass Betaserc ein wirksames Arzneimittel darstellt. Eine Nicht-Vergütung kommt daher von vornherein nicht in Betracht. Vor diesem Hintergrund sind Preisbildung und Kosten gesetzlich definiert. Translation: We are surprised that the questions are being assessed as part of the BAG's work to define health insurance coverage. It may be interesting for clinicians and patients to examine Betaserc - like any other drug - in more detail in a comprehensive review. From the OKP perspective, however, the HTA appears obsolete because the essential findings with regard to an obligation to pay can be collected very quickly. For example, a look at the Swissmedic approval combined with an evaluation of recent studies (e.g. Christine Adrion et al., "Efficacy..." in BMJ 2016;352:h6816) would provide sufficient information about Betaserc's WZW conformity. The result of this HTA can therefore already be predicted ex ante to a degree that makes the implementation of HTA an unnecessary use of resources. Betaserc is an approved medicine, so it is effective, safe and of good quality. Its effect and its extent of effect may indicate the need for further research in the HTA results. But the current data shows that Betaserc is an effective drug even without HTA. Non-remuneration is therefore out of the question from the outset. Against this background, pricing and costs are defined by law.	As part of the HTA process, the plausibility of the topic has been scrutinized and an evaluation of the topic has been recommended by the Eidgenössische Kommission für allgemeine Leistungen und Grundsatzfragen (ELGK) and Eidgenössische Arzneimittel-Kommission (EAK). The publication mentioned will be included in the HTA provided if it fulfils the inclusion criteria.
3	In the part for effectiveness/efficiousness and safety only three different databases with completed studies will be searched through. The inclusion of further databases should be considered.	It has been decided not to search for peer-reviewed articles in additional databases, because in general there is much overlap between databases. In addition to the search in PubMed (MEDLINE), Embase.com and Cochrane Library, reference lists of selected reviews and the included studies will be checked for potentially missed articles. No change needed.
3	It is not clear whether, among other things, guidelines (at least for information) or already conducted HTAs will also be consulted for the part of effectiveness/efficiousness and safety. These should also be taken into account.	Relevant guidelines as well as reviews and HTAs will be considered in the sections “Additional Issues” and “Discussion” of the planned HTA report and used to put the evidence identified into context. A systematic search for these evidence syntheses is not planned though. No change needed.

3	We suggest that direct comparative studies between the above-mentioned medicines should also be included.	Direct comparisons between drugs are out of scope for the current HTA. No change needed.
3	The outcome parameters are not well specified. It is not clear whether associated sympomatics are also considered, for example in the case of "vertigo" (nausea, etc.).	The description of the outcome was left relatively broad in order to be able to include different formats of relevant data. In keeping with the GRADE methodology we have limited the number of outcomes to be assessed to those deemed the most important ones by the Swiss clinical experts we consulted. Symptoms such as the nausea will therefore not be assessed as separate effectiveness outcomes, but they will be indirectly included in outcomes on health-related quality of life. No change needed.
3	It can also be assumed that the diagnostic procedures used for tinnitus and vertigo vary from study to study. The patient's perception and assessment also plays an important role (subjectivity). These aspects should be taken into account.	Agreed. These data will be extracted from the included studies and will be taken into account in the risk of bias assessment. No change needed.
3	The procedure for the economic evaluation of the medication mentioned is well presented. The relevant points are addressed.	No change needed.
4	With regards to the use of betahistine, study protocols that investigated off-label use, especially higher doses than proposed by the manufacturer and the combined use with MAO-B inhibitors should be taken into account as well in the planned HTA project. This will provide important additional information about the use of betahistine in current practice and thus may help to estimate its value in treating patients with Menière's disease and other disorders.	There are no exclusion criteria concerning dosage. However, regulatory decisions can only be made for indications and dosages a drug is licensed for. Therefore, results from or including studies with off-label dosages will be presented as additional information.. No change needed.
4	From the neurological perspective, there should be paid special interest to review also the literature reporting on the use of betahistine and cinnarizine with or without dimenhydrinate for the treatment of vertigo due to other peripheral or central vestibular disorders. This is especially true for the combined treatment with cinnarizine and dimenhydrinate (on label for "symptomatic treatment of transient vertigo") that potentially affects patients with various neurological disorders.	Agreed. The text in the protocol has been changed.
5	Page 14 and 19 (Exclusion criteria): ELS surgery is not destructive. We recommend to not exclude this patient group. If these patients are included, then they should be represented in both, the betahistin and the control group.	Agreed that the term "destructive" only refers to medical treatment. However, this patient group will still be excluded, as this HTA focuses only on non-destructive medical treatments. Therefore, for clarity, this exclusion criterion will be adapted in the HTA report as follows: "Patients who had already undergone destructive medical (e.g. intratympanic gentamicin) or surgical treatment (e.g. endolymphatic sac surgery, labyrinthectomy and vestibular neurectomy)".
5	Meniere's disease (MD) is closely related to migraine. About half of all MD- patients also have migraine (Ghavami Y et al. Laryngoscope, 126:163-168, 2016). Since cinnarizine, like flunarizine (which should actually also be studied for its efficacy against MD) has also been shown to be effective as a migraine prophylactic according to a recent review, it is imperative that all patients with MD should have been asked about migraine symptoms. If this was not done, these studies should be reviewed critically. Unfortunately, this did not happen in the clinical trial conducted by Adrion C, Strupp et al (BMJ 2016). Betahistine might trigger migraine because, although in principle it is a histamine antagonist, it is in fact a histamine agonist because it blocks the receptor that blocks the reuptake of the released	Agreed. In the discussion of the HTA report, the potential confounding effect of migraine on the results will be discussed.

	histamine into the cell. Thus, if histamine is going to exacerbate migraine and thus MD symptoms in patients with both, MD and concomitant migraine, (50% of patients: it would be not beneficial due to migraine, but would be beneficial in the other half), then it would be important to explain why it is not better than placebo when only MD is considered. The review should examine all existing scientific work and distinguishing between MD and migraine. The authors of the HTA should consider a lack of discrimination between MD and migraine as a disadvantage and at the very least, this reduces the evidence. After all, it could be that cinnarizine helps patients with MD and migraine much better than those with MD only. It might even be effective in only one group. Analysis of subgroups, MD alone and Meniere's disease/migraine combined, is crucial.	
5	Minor correction Page 26: Citation 6: Journal of vestibular research (not VES).	Agreed. This will be corrected in the HTA report.
6	The combination of cinnarizine and dimenhydrinate can treat peripheral-vestibular, central-vestibular as well as combined peripheral and central-vestibular vertigo. Therefore, we request that the term "vestibular vertigo" be replaced with "peripheral and central vestibular vertigo" throughout the document and in the tables.	Agreed. The text in the protocol has been changed.
6	Because of the synergistic effects, the fixed-dose combination allows a reduction in the dose of the two drugs compared with the respective monotherapies, resulting in a reduction in side effects due to increased efficacy. This should be taken into account when comparing the data and doses of the cinnarizine-dimenhydrinate fixed combination with the monotherapies.	For all drugs, data regarding dosages, effectiveness, and adverse events will be extracted. In the economic model recommended dosages as specified by Swissmedic will be used. It will be checked whether the prescribed dosages in the included studies align with the recommended dosages.
6	The sentence "Furthermore, cinnarizine with dimenhydrinate (another antihistamine) is being reimbursed for the symptomatic treatment of transient vertigo" is incorrect and should be replaced with "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"	Agreed. The text in the protocol has been changed.
6	"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 other disorders." should be replaced with "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 other vestibular disorders."	Agreed. The text in the protocol has been changed.
6	This section is very limited to Ménière's disease and should be updated. As stated in the executive summary, the fixed combination of cinnarizine and dimenhydrinate is reimbursed for the symptomatic treatment of transient vertigo. This includes more than Ménière's disease. Cinnarizine, as a calcium channel blockers, inhibits the calcium influx into the vestibular sensory cells acting predominantly on the peripheral vestibular system. Dimenhydrinate, as an antihistamine, acts predominantly on the central vestibular system. Both actives in the fix combination cause a reduction in symptoms of vertigo of various origins beyond Ménière's syndrome and disease.	Agreed. The following sentence has been added to the protocol: "Benign paroxysmal positional vertigo and vestibular neuronitis are considered to be the most common (peripheral) causes of vestibular vertigo". A more detailed description will be included in the HTA report.

6	Trials with betahistine and cinnarizine as monotherapy as comparator should also be included in both the clinical and economic evaluation studies.	Since the evidence for the effectiveness of betahistine and cinnarizine is in question, they should not be used as comparators. In other words, their effectiveness must be demonstrated before they can be included as comparators. No change needed.
6	In addition, the Mean Vertigo Score (MVS) should be included as a possible primary outcome. The Mean Vertigo Score (MVS) outcome scale, which has been used as primary efficacy endpoint in clinical research for 30 years, is a composite endpoint developed for measuring the degree of vertigo in patients suffering from various vestibular disorders. A recent validation study can be downloaded at The Mean Vertigo Score (MVS) Outcome Scale and Its Use in Clinical Research for Quantifying Vestibular Disorders - PubMed (nih.gov).	Vertigo is included as one of the outcomes of interest. The instruments used are not specified for any outcome. Any validated instruments and outcome measures will be extracted as reported in the studies. No change needed.
6	Concomitant vegetative symptoms should also be considered as possible secondary outcome, as these can have a major impact on patient QoL.	Effects on concomitant vegetative symptoms are deemed to be already accounted for via the assessment of patient quality of life outcomes. As such, they are already included in the HTA as an outcome. No change needed.
6	The search terms (Appendices 9.1 and 9.2) should also be complemented by the words “peripheral” and “central”. Arlevert* and the fixed combination should be added to the intervention sting. Furthermore, betahistine or the mono component cinnarizine can only be used to treat peripheral-vestibular vertigo. Therefore, the fixed combination has a wider range of indications that need to be considered in this HTA.	Agreed. The search term "Arlevert" has been added. However, the other suggested search terms will not be added as they are already encompassed by existing (MeSH) terms like "Vertigo" and would limit rather than broaden the search.