Consolidated stakeholder feedback

HTA report

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

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

1	Santésuisse
2	Schweizerische Gesellschaft für Oto-Rhino-Laryngologie, Hals- und Gesichtschirurgie
3	Swiss Neurological Society (SNS)
4	Viatris Pharma GmbH

SH	SH comment	Reply authors / BAG & implemented changes
1	The analysis of the defined research question on treatment with Betahistin or Cinnarizin with or without Dimenhydriat for Morbus Menière as well as for symptoms of vestibular vertigo and tinnitus is presented comprehensively and in detail. The results for the four different therapy groups described, which are based on the marketing authorisations of the medicinal products in Switzerland, clearly show that there is hardly any evidence for the effect of these drugs. Only the combination of cinnarizine with dimenhydrinate can be assumed to have a certain possible efficacy against symptoms of vertigo based on two different studies. However there were no outcomes reported with regard to tinnitus or health-related quality of life. Moreover, the duration of therapy was only four weeks. The results found are also reflected in the national and international guidelines, where these drugs are mentioned in some cases, but the efficacy of betahistine in particular is assessed as unclear and unproven. We clearly support the considerations regarding costs, cost-effectiveness and budget impact. The future reimbursement of these medicinal products in the indications analysed must therefore be seriously questioned. These discussions should be held as soon as possible in order to avoid further unnecessary	Thank you very much for your feedback regarding the report and your input. No change to the report needed.

	burdens on health insurance dispite a lack of evidence. For this reason, the results of the ongoing study with betahistine should not be awaited, as the end date of the study is not known. In addition, it can be assumed that restricting or cancelling the reimbursement of these drugs by the compulsory health insurance due to a lack of evidence is unproblematic from an ethical, social, legal or organisational point of view.	
2	Die Arbeitsgruppe Neurootologie der schweizerischen Gesellschaft für Oto-Rhino-Laryngologie, Hals- und Gesichtschirurgie hat den HTA-Bericht ausführlich geprüft. Eine Mehrheit der Gruppe spricht sich dafür aus, die Kostenerstattung für Betahistin sowie Cinnarizin (+/- Dimenhydrinat) beizubehalten, um die Patienten weiterhin angemessen zu unterstützen, trotz der anerkannten methodischen Bedenken. Evidenzlage und Methodik: Die Evidenz für die Wirksamkeit von Betahistin und Cinnarizin (+/- Dimenhydrinat) bei Morbus Ménière und vestibulärem Schwindel ist begrenzt und weist methodische Schwächen auf. Viele Studien haben kleine Stichproben, veraltete Diagnosekriterien und inkonsistente Endpunkte. Ein Großteil der Forschung wurde vor Jahrzehnten durchgeführt und entspricht nicht mehr den heutigen Standards. Trotz dieser Schwächen zeigen einige Studien, wenn auch mit sehr geringer Evidenzsicherheit, dass Betahistin und Cinnarizin (+/- Dimenhydrinat) einen positiven Effekt auf die Reduktion von Schwindelanfällen und die Verbesserung der Lebensqualität haben können. Beispielsweise zeigte Betahistin in einer randomisierten kontrollierten Studie eine signifikante Verbesserung der Lebensqualität im Vergleich zu keiner Behandlung, und Cinnarizin mit Dimenhydrinat führte bei verschiedenen Schwindelursachen zu einer signifikanten Symptomverbesserung im Vergleich zu Placebo. Sicherheitsprofil und klinische Relevanz: Die Medikamente haben ein günstiges Sicherheitsprofil und sind mit geringen Risiken schwerwiegender Nebenwirkungen verbunden. Betahistin wird gut vertragen, während Cinnarizin und Dimenhydrinat hauptsächlich leichte, handhabbare Nebenwirkungen aufweisen. Klinische Erfahrungen und Patientenberichte legen nahe, dass diese Medikamente für viele Patienten eine spürbare Verbesserung der Lebensqualität bringen. Obwohl die wissenschaftliche Evidenz begrenzt ist, sollte der klinische Nutzen, den viele Patienten erfahren, nicht ignoriert werden. Bedeutung der Kostenerstattung: Die Mehrheit der Arbeitsgruppe ist der Ansicht, dass die Streichung der Kostenerstattung zu einer erheblichen Einschränkung der Behandlungsmöglichkeiten für Patienten führen würde, die unter den oft stark beeinträchtigenden Symptomen von Morbus Ménière und vestibulärem Schwindel leiden. Diese Erkrankungen haben einen erheblichen Einfluss auf die Lebensqualität, und die Therapieoptionen sind begrenzt. Eine Aufhebung der Kostenerstattung würde den Zugang zu diesen Behandlungen erschweren und könnte die Lebensqualität der betroffenen Patienten erheblich verschlechtern. Forschung und Zukunftsperspektiven: Die Arbeitsgruppe erkennt den Bedarf an weiteren, qualitativ hochwertigen Studien an, die aktuelle diagnostische	Thank you very much for your feedback. No change to the report needed.

	Kriterien und gut definierte patientenberichtete Endpunkte (PROMS) verwenden. Solche Studien sind notwendig, um zukünftig fundiertere Entscheidungen zur Kostenerstattung treffen zu können. Bis solche Daten verfügbar sind, sollte die Kostenerstattung jedoch fortgesetzt werden, um den betroffenen Patienten weiterhin eine angemessene Behandlung zu ermöglichen. Schlussfolgerung: Die Arbeitsgruppe Neurootologie plädiert mehrheitlich dafür, die Kostenerstattung für Betahistin und Cinnarizin (+/- Dimenhydrinat) beizubehalten. Trotz der methodischen Bedenken sprechen das günstige Sicherheitsprofil und die positiven klinischen Erfahrungen dafür, dass diese Medikamente weiterhin eine wichtige Rolle in der Behandlung von Morbus Ménière und vestibulärem Schwindel spielen sollten. Eine Aufhebung der Kostenerstattung könnte die Lebensqualität der betroffenen Patienten erheblich beeinträchtigen und den Zugang zu wichtigen Therapieoptionen unnötig einschränken. Translation: The Neurotology Working Group of the Swiss Society for Otorhinolaryngology, Neck and Facial Surgery has examined the HTA report in detail. A majority of the group is in favor of maintaining reimbursement for betahistine and cinnarizine (+/- dimenhydrinate) in order to continue to support patients appropriately, despite the recognized methodological concerns. Evidence and methodology: The evidence for the effectiveness of betahistine and cinnarizine (+/- dimenhydrinate) in Ménière's disease and vestibular vertigo is limited and has methodological weaknesses. Many studies have small samples, outdated diagnostic criteria and inconsistent endpoints. Much of the research was conducted decades ago and no longer meets today's standards. Despite these weaknesses, some studies, albeit with very low certainty of evidence, show that betahistine and cinnarizine (+/- dimenhydrinate) can have a beneficial effect on reducing dizziness and improving quality of life. For example, in a randomized controlled trial, betahistine showed a significant improvement in quality of life compared to no treatment, and cinnarizine with dimenhydrinate resulted in significant symptom improvement compared to placebo for various causes of dizziness. Safety profile and clinical relevance: The drugs have a favorable safety profile and are associated with low risks of serious side effects. Betahistine is well tolerated, while cinnarizine and dimenhydrinate have mainly mild, manageable side effects. Clinical experience and patient reports suggest that these drugs provide a noticeable improvement in quality of life for many patients. Although scientific evidence is limited, the clinical benefit experienced by many patients should not be ignored. Importance of reimbursement: The majority of the working group believes that removing reimbursement would significantly limit treatment options for patients suffering from the often debilitating symptoms of Ménière's disease and vestibular vertigo. These conditions have a significant impact on quality of life and treatment options are limited. Removing reimbursement would make access to these treatments more difficult and could significantly worsen the quality of life of affected patients. Research and future prospects: The working group recognizes the need for further high-quality studies using	

	current diagnostic criteria and well-defined patient-reported outcomes (PROMS). Such studies are necessary to make more informed reimbursement decisions in the future. However, until such data are available, reimbursement should be continued to enable affected patients to continue to receive appropriate treatment. Conclusion: The majority of the Neurotology working group advocates maintaining reimbursement for betahistine and cinnarizine (+/- dimenhydrinate). Despite the methodological concerns, the favorable safety profile and positive clinical experience suggest that these drugs should continue to play an important role in the treatment of Ménière's disease and vestibular vertigo. Removal of reimbursement could significantly impair the quality of life of affected patients and unnecessarily limit access to important treatment options.	
3	In summary, the HTA report provides a systematic review on the efficacy, effectiveness, safety, cost-effectiveness and budget impact. Key results are summarized below. For betahistine (compared to placebo) in the treatment of Menière's disease no statistically significant differences were found in vertigo attack frequency, tinnitus intensity and hearing loss, but also no differences were noted in patient-related outcome measures related to quality of life. Furthermore, evidence on the effect of betahistine on diverse vertigo aetiologies compared with placebo was lacking, seemed not consistent and was very uncertain. Likewise for the treatment of idiopathic tinnitus with cinnarizine vs. placebo no statistically significant differences were noted. For the treatment of diverse vertigo etiologies with cinnarizine and dimenhydrinate a statistically significant improvement of vertigo symptoms was observed. Cost-effectiveness for treating vertigo caused by other disorders than Meniére's disease was confirmed. A budget impact of CHF 0.4 Million for the use of cinnarizine with dimenhydrinate over 5 years was calculated. The SNS considers the quality of the report as high. Specifically, the methodology is clearly described and the data analysis is sound. The aims defined are addressed appropriately. Specifically, the SNS appreciates that the use of cinnarizine and dimenhydrinate for the treatment of vertigo other than Menière's disease was included in the analysis. The SNS believes that this report will be very valuable in the discussion whether betahistine and cinnarizine with or without dimenhydrinate should be reimbursed by the Swiss compulsatory health insurance or not for Menière's disease, idiopathic tinnitus and the treatment of diverse vertigo aetiologies other than Menière's disease. Based on the results presented here and under the premise that treatment strategies should always be evidence-based, the SNS supports the re-evaluation of betahistine reimbursement for treating Menière's disease and also is in favor of prioritizing other, evidence-based treatments instead of betahistine. Taking into account also the estimated budget impact of betahistine of CHF 17.2 Millions (over 5 years) for the treatment of Menière's disease, a change in the reimbursement policy for betahistine may result in significant savings. Thus, the SNS believes that based on the current evidence continuation of reimbursement of betahistine for treating Menière's disease is not justified. Likewise,	Thank you very much for your feedback regarding the report and your input. No change to the report needed. Note: Based on newly available input, the budget impact analysis for cinnarizine with dimenhydrinate was updated. The updated budget impact analysis showed that cinnarizine with dimenhydrinate resulted in a projected budget net saving of CHF 1.2 million over a 5-year period. The initial estimate remained a scenario in the report.

	considering lack of evidence on the treatment effect of betahistine for diverse vertigo aetiologies, the use of betahistine for this condition is not recommended and thus also no reimbursement should be made. For the use of cinnarizine in the treatment of idiopathic subjective tinnitus in adults the evidence identified in the HTA report was very uncertain and the difference in tinnitus symptoms compared to placebo seemed to be little or absent. At the same time data on serious side effects is lacking. The estimated budget impact of cinnarizine without dimenhydrinate was CHF 0.8 Million over 5 years. Thus, the SNS believes that based on current evidence the reimbursement of cinnarizine without dimenhydrinate for the treatment of idiopathic subjective tinnitus is not justified. With regards to the use of cinnarizine with dimenhydrinate for the treatment of diverse vertigo etiologies for a maximum of 4 weeks, a treatment effect in comparison to placebo was confirmed (moderate certainty evidence). Thus, the SNS recommends to keep the current practice, i.e. to continue reimbursement by the Swiss compulsatory health insurance for the acute treatment of vertigo of diverse etiologies with cinnarizine and dimenhydrinate over a maximum of 4 weeks.	
4	Seit über 50 Jahren (1973) ist Betaserc in der Spezialitätenliste aufgenommen. Betaserc wird alle drei Jahre im Rahmen der Überprüfung der Aufnahmebedingungen hinsichtlich (u.a.) seiner Wirksamkeit überprüft. Diese Wirksamkeit wurde bislang nie in Zweifel gezogen. Ein HTA, das lediglich eng vordefinierte RCTs widergibt, ist eine Zusammenfassung des Offensichtlichen und damit inhaltlich ohne Novität. Sein Sinn und Zweck dürfen hinterfragt werden. «Stating the obvious» greift auch bei einem HTA zu kurz. Die Studienlage ist bekannt. Ein HTA kann diese Studienlage ergänzen. Ein Bericht nur über die bereits hinlänglich bekannte Studienlage ist kein HTA, wie es gemeinhin international verstanden wird. Nach Schweizer Recht, welches das Instrument «HTA» nicht näher definiert, ist ein HTA basiert auf bekannten klinischen Studien bedeutungslos. Betahistin hat sich während mehr als fünf Jahrzehnten in der klinischen Praxis bewährt. Betahistin ist in den Richtlinien der Schweizer Spitäler zur Behandlung des Morbus Menière verankert und auf den Arzneimittellisten dieser Einrichtungen aufgeführt. Europäische KOLs im Therapiesegment des Schwindels raten dazu, weiterhin Patienten mit häufigen und beeinträchtigenden Menière-Attacken mit Betahistin zu behandeln. Betahistin wird welt- bzw. europaweit einhellig in Leitlinien empfohlen. Angesichts der nicht eindeutigen Literatur wurden anlässlich von nationalen, internationalen und interkontinentalen Konsensus-Konferenzen mit Experten Best-Practice-Kriterien für die Therapie des Ménière-Syndroms definiert. Sie bestätigen, dass der Einsatz von Betahistin zur Behandlung des Ménière-Syndroms als Erstlinientherapie breit unterstützt wird. In den meisten europäischen Ländern ist Betahistin verfügbar und für die Behandlung von Schwindelanfällen und Ménière-Syndroms vergütet. In keinem Land ist Betahistin von der Erstattungspflicht ausgenommen worden in den letzten Jahren. Das BAG hat in den Jahren 2019 und 2022 die WZW-Kriterien von Betahistin überprüft und dabei die	Thank you very much for your feedback. As already stated in the rebuttal of the stakeholder comments regarding the protocol process the plausibility of the topic has been scrutinized and an evaluation of the topic has been recommended by the federal commission for general services and principles and federal pharmaceutical commission as part of the HTA process. Regarding the endorsement of the therapies in the clinical community the controversy of these treatments has been confirmed by the clinical experts consulted. Since data reporting in the included RCTs was limited, it was not expected that a search for non-randomised studies would result in additional relevant evidence. We have reformulated the text in section 6.1. so that the rationale for the focus on randomised controlled trials is clearer.

	Wirksamkeit nie in Frage gestellt. Seit der letzten Überprüfung sind keine neuen Erkenntnisse zu Betahistin publik geworden oder haben zu einer Anpassung der Fachinformation geführt. Auch gibt es keine neuen Therapieoptionen für die betroffenen Patienten. Es ist deshalb bereits die Vorfrage, warum Betahistin einer HTA-Analyse unterzogen werden soll, nicht nachvollziehbar: Wenn ein Arzneimittel alternativlos ist, und wenn zumindest ein (notabene grosser) Teil der klinisch tätigen Experten eine Wirksamkeit erkennt und als wesentlich erachtet, dann erübrigt sich ein HTA; insbesondere eines, dass wie eingangs festgehalten, ohne neue Erkenntnisse ist, und dies schon von vornherein aufgrund der Untersuchungsanlage offensichtlich war. Betahistin ist gemäss einhelliger Expertenmeinung, publiziert in Guidelines und in Konsens-Statements, weltweit eine Therapieoption, auf die man nicht verzichten kann. Patienten würden ohne Not einer Behandlung beraubt, die in vielen Fällen hilft. Insgesamt sprechen multiple Gründe für die Vergütung von Betahistin durch die OKP: • Seit über 50 Jahren in den meisten Ländern zugelassen und erstattet. • Klinischer Konsens, verankert in Guidelines und Konsensus-Papieren. • In Schweizer Spitälern auf der Medikamentenliste und in Therapieempfehlungen. • Gute Verträglichkeit, bei Komorbiditäten mit anderen Arzneimitteln kombinierbar. • Keine gleichwertigen Therapiealternativen. • Geringe Kosten. Die HTA-Fragestellung war ab initio fragwürdig. Cui bono? Das Resultat war absehbar. Es war ex ante offensichtlich, dass selbst ein noch kritischeres Verdikt keine Konsequenz haben darf. Die Alternative zur Nicht-Konsequenz, d.h. die Nicht-Vergütung von Betahistin liesse ein Therapievakuum entstehen. Dieses ist nach sehr breit abgestützter ärztlicher Einschätzung (Leitlinien und Konsensus-Statements) das wesentlich grössere Übel als die Möglichkeit, mit Betahistin nicht bei jedem Patienten erfolgreich therapieren zu können. Translation: Betaserc has been included in the specialty list for over 50 years (1973). Betaserc is reviewed every three years as part of the review of the admission conditions with regard to (among other things) its effectiveness. This effectiveness has never been called into question. An HTA that only reflects narrowly predefined RCTs is a summary of the obvious and therefore has no novelty in terms of content. Its meaning and purpose can be questioned. "Stating the obvious" is also insufficient for an HTA. The study situation is known. An HTA can supplement this study situation. A report only on the already sufficiently known study situation is not an HTA as it is generally understood internationally. According to Swiss law, which does not define the "HTA" instrument in more detail, an HTA based on known clinical studies is meaningless. Betahistine has proven itself in clinical practice for more than five decades. Betahistine is anchored in the guidelines of Swiss hospitals for the treatment of Meniere's disease and is included on the drug lists of these institutions. European KOLs in the dizziness therapy segment recommend continuing to treat patients with frequent and debilitating Menière's attacks with betahistine.	

	Betahistine is unanimously recommended in guidelines worldwide and throughout Europe. In view of the ambiguous literature, best practice criteria for the treatment of Menière's syndrome were defined at national, international and intercontinental consensus conferences with experts. They confirm that the use of betahistine to treat Menière's syndrome as first-line therapy is widely supported. In most European countries, betahistine is available and reimbursed for the treatment of dizziness and Menière's syndrome. In no country has betahistine been exempted from reimbursement in recent years. The BAG reviewed the WZW criteria for betahistine in 2019 and 2022 and never questioned its effectiveness. Since the last review, no new findings on betahistine have been made public or have led to an adjustment of the product information. There are also no new treatment options for the affected patients. The preliminary question of why betahistine should be subjected to an HTA analysis is therefore incomprehensible: If there is no alternative to a drug, and if at least a (large) proportion of clinically active experts recognize its effectiveness and consider it to be essential, then an HTA is unnecessary; especially one that, as stated at the beginning, contains no new findings, and this was obvious from the outset due to the study design. According to unanimous expert opinion, published in guidelines and consensus statements, betahistine is a treatment option worldwide that cannot be dispensed with. Patients would be unnecessarily deprived of a treatment that helps in many cases. Overall, there are several reasons for betahistine to be reimbursed by the OKP: • Approved and reimbursed in most countries for over 50 years. • Clinical consensus, anchored in guidelines and consensus papers. • On the medication list in Swiss hospitals and in treatment recommendations. • Well tolerated, can be combined with other drugs in the case of comorbidities. • No equivalent treatment alternatives. • Low costs. The HTA question was questionable from the outset. Cui bono? The result was foreseeable. It was obvious ex ante that even an even more critical verdict should not have any consequences. The alternative to no consequences, i.e. non-reimbursement of betahistine, would create a treatment vacuum. According to very broadly supported medical assessment (guidelines and consensus statements), this is a much greater evil than the possibility of not being able to successfully treat every patient with betahistine.	