HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

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Response to

- the Statement from Inspire Medical Systems Europe GmbH [1] (dating September 20th 2022) and
- the Letter from the Austrian Sleep Research Association/ASRA (dating September 30th 2022)

on the 2nd Update of AIHTA DSD 100 on "Upper airway stimulation for moderate-to-severe sleep apnea", which was conducted in the context of the annual maintenance of the Austria hospital benefit catalogue.

We highly appreciate the critique expressed by the manufacturer of the device and the Board of Directors of the Austrian Sleep Research Association[1] , which we take as an opportunity for a critical appraisal and scientific debate.

We perceive a significant misunderstanding which is two-fold:

- First, the authors of the AIHTA report assessed the evidence as *insufficient* for the adoption into the Austrian hospital benefit catalogue for standard reimbursement. For the purpose of documentation, hypoglossal nerve stimulation (HGNS) was included with an XN-code. Given that the intervention is already in use in Austria, this is an optional response of the decision-makers (LKF- Arbeitskreis) to our GRADE-based evidence-based recommendation to further collect data[2] on the respective intervention [2].
- Second, it is important to stress that *insufficient evidence* to support standard reimbursement should not be confused with evidence for no effect. In this context, it is not illogical that evidence-based guidelines recommend an intervention based on low-certainty evidence while the exact same evidence is considered insufficient to support inclusion into standard reimbursement [3, 4]. Although there are some data of very low certainty with regard to the effectiveness of the device, long-tem evidence derived from large registries proving that the device is safe is absent.

Further, the authors of any HTA report conducted by AIHTA consult with a clinical expert. However, it is mandatory that these clinical experts are free from conflicts of interest/ CoI. An association with the manufacturer (e.g., consulting fees) is an exclusion reason to be considered as an external reviewer of our reports.

[1] The president of ASRA, Priv.-Doz. Dr. Michael Saletu was a consultant to Inspire Medical Systems Europe GmbH, declared to have CoI due to having received honoraria as Speaker or Consultant for several companies, incl. Inspire.: https://www.kup.at/kup/pdf/14765.pdf

[2] in 2023, 16 XN-Codes are listed: Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz. LKF-Modell 2023 (https://www.sozialministerium.at/Themen/Gesundheit/Gesundheitssystem/Krankenanstalten/LKF-Modell-2023.html) [accessed 24.10.2022]

We appreciate the scientific debate that improves the quality of our and other HTA reports to deliver patients safe and effective technologies. Hence, we translated the critique into English and formulated our reaction to it. The criticism and our response are structured into eight points and can be found below.

With our best wishes,

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Response to Inspire Statement and ASRA Letter

No.	Point of criticism (translated)	Response: Authors' reply
1	Exclusion of the EFFECT study from the effectiveness evaluation (pp. 4 - 5)	We appreciate this critique. It is correct that RCTs are the gold standard for evaluating effectiveness [5, 6]. From a theoretical perspective, we acknowledge that excluding RCTs can be seen as a deviation from the "best available evidence" principle. However, according to the Cochrane Collaboration, "(…) crossover trials may be excluded if the design is inappropriate to the clinical context. Very often (…), it is difficult or impossible to extract suitable data from a crossover trial [7]." The EFFECT study [8] is a crossover trial with significant limitations regarding wash-out period and reporting of data to be extracted. All patients had a UAS implant for at least six months and received therapeutic stimulation at baseline. The risk of bias (RoB) assessment of this trial revealed that the study has a high RoB, and the study was, hence, excluded from the evaluation of the effectiveness of the device. Although there was no statistical evidence for a carry-over effect within the time period under investigation, there was no defined wash-out period which is usually done in high-quality crossover trials [9, 10]. The inclusion of both responders and non-responders in the trial is a clear strength of the EFFECT trial [8]. However, all patients received device therapy six months before the trial. Hence, the risk that non-responders or non-compliant patients may have not entered the study in the first place may be increased and that the observed effects might only be valid for a pre-selected group of patients. The fact that it was impossible to extract suitable data from the EFFECT study [8] (e.g., no comparative data without any UAS available) further supported our decision not to consider it in the evaluation of the effectiveness of the device. The limitations of both study design and reporting were further supplemented with a long list of conflicts of interest of the EFFECT trialists [8], resulting in overall major doubts with regard to the credibility of the trial. Regardless of the aforementioned reasons for not having included the trial, we acknowledge that it would have also been a viable route to include the trial and present the inconclusive evidence derived from this trial in our report. However, the conclusion regarding effectiveness and safety would not have changed.

2	AHI responders in the control group - a placebo effect as a reason for exclusion? (pp. 5 – 6)	We fully agree with this critique: Too much emphasis has maybe been placed on the placebo effect in the discussion section. Nevertheless, that was not the reason for exclusion. The reason for exclusion was the design of the study (more details described above).
3	Positive evaluation by the HAS in France Inclusion in the list of products and benefits of the French Social Security Code *(Code de la sécurité sociale)* (pp. 6 – 7)	We acknowledge that different HTA institutions came to slightly different conclusions. The mentioned report from CNEDIMTS [11] judged the evidence as sufficient for reimbursement as a third line therapy in certain patients: *"The Commission recommends a registration under a brand name and retains the following indications:* *Treatment of moderate to severe obstructive sleep apnea-hypopnea syndrome (OSAHS) (15 ≤ AHI ≤ 50) in patients with a BMI less than 32 kg/m² and in treatment failure (non-responders or non-observers) by continuous positive airway pressure (CPAP) and mandibular advancement orthosis (MAO) within the indications defined by the LPPR[3]."* Still, it is noteworthy to highlight some other recent evaluations conclude nearly identical on the available evidence: • **EUnetHTA 2020:** "The quality of the evidence was very low, both for effectiveness and safety" [12] • **NIPH 2022**: "The effect of hypoglossal nerve stimulation in the treatment of obstructive sleep apnea is generally very uncertain" [13] Each health system has different criteria for medical services to be included in DRG systems. To learn more about both different evidence based reimbursement processes (incl. different requirements in European health systems), we recommend to consult MTRC [14]. It provides information which evidence is required for reimbursement in different countries. With regard to the AIHTA report 2022 [15] conducted to support an evidence based reimbursement decision for the hospital benefit catalogue in Austria, the authors assessed the available evidence to be inconclusive and, hence, a "currently not" recommendation was given. This evidence-based recommendation resulted in the inclusion of the device into the hospital benefit catalogue as a new examination and treatment method ("Neue Untersuchungs- und Behandlungsmethode/ NUB"; XN-Codes) for the purpose of documentation. This is aligned with the ideal types of how evidence based recommendations translate into decision making and finally evidence-based clinical pratice(for more details, see [2]), that the implementation is accompanied with data documentation in research settings (such as university hospitals). For this purpose, the legislator provides for the compensation of the additional clinical expenditure (Abgeltung des klinischen Mehraufwands).
4	Care of patients with HGNS in	We fully agree. One may want to add that such a novel technology should not only be used in specialised centres but also as part of clinical

[3] Liste des produits et prestations remboursables (list of reimbursable products and services)

	specialised interdisciplinary centres (p. 7)	research to generate the required evidence also with regard to long-term safety of the device (see response on 3.).
4.1	Total number of patients indicated (p. 7)	We fully agree that summarising the total number of patients may include patients enrolled in multiple studies. The true total number of patients is likely to be smaller. Still, transparent reporting on which patients a study/ publication of a study refers to is desirable.
4.2	Contradiction between the desire to create specialised centres and the desire for the perfect scientific location (p. 7)	This must be a misunderstanding; As mentioned above, there is no contradiction between specialised centres and the generation of evidence in clinical practice. Instead, these specialised centres could use all patients as part of their research. We support specialised centres for patients with OSA.
5	Misleading summary of guideline recommendations (pp. 8 – 9)	We want to highlight that this HTA report [15] is an update of the evidence. A guideline synopsis was not undertaken. Hence, evidence-based guideline recommendations were briefly described narratively described in the discussion section. We would like to thank the authors of the critique for noticing a small omission with regard to the German AWMF S3 [16] recommendation: The level of evidence was wrongfully not stated in the report. The correct recommendation is: *"Neurostimulation of the hypoglossal nerve should be considered in patients with CPAP intolerance or ineffectiveness with an AHI 15-65/h and a BMI up to 35 kg/m2 and in the absence of anatomical abnormalities and moderate to severe OSA (evidence level 1b, recommendation grade B)."* This was a simple omission that can occur within such an HTA report. However, we apologise for this omission. The quotation marks, which surrounded the word certain, did not have a negative connotation as it may have appeared. The quotation marks should highlight that the recommendation does not apply to all patients, but only to a highly selected subgroup of patients who meet the relevant requirements. Speculation with regard to concluding that AIHTA is not neutral based on one error in the discussion section seems a bit far fetched.
6	Classification of the evaluation by NICE in England (pp. 10 - 11)	Again we did not summarise guidelines systematically. It is noteworthy to mention that the authors of the critique have provided such a detailed description of the assessment of the four categories according to NICE [17], although such a detailed description is not provided in the discussion. The NICE report states: "*Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate-to-severe obstructive sleep apnoea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research"*.

		As stated in 3 the device is now included in the Austrian hospital individual services catalogue as a new examination and treatment method for the purpose of documentation.
7	Safety of the procedure (pp. 11 - 12)	As described in the report, there are data on the safety of the device mainly from observational studies [18, 19], as the RCTs [8] duration was too short (2 weeks only). We acknowledge that a registry study over several years is appropriate for the safety assessment. Interim results of the ongoing ADHERE register study were included in the analysis of our report [19].The authors of the report are aware that 2.3% of the 1849 patients reported serious adverse events at the time of data analysis. It is also known that 19% of patients with available follow-up data reported therapy-related discomfort, defined as stimulation-related discomfort, insomnia/arousal, or tongue abrasion. However, it should also be considered that follow-up data (1 to 2 years follow-up) were only available from 823 patients (corresponding to a loss-to-follow-up of 55,5%). The ongoing ADHERE study (NCT02907398) [20] enrolled 5000 patients and will be completed in 2024 and may provide more safety data. Suffice it to say that transparent reporting on loss to follow up and specifics on data evaluation is necessary. Overall, in the two included observational studies [18, 19] several serious adverse events (SAEs, intraoperative and during follow-up) occurred, most of which (73%) were due to serious adverse product-related events (SADEs: sensor lead revision, stimulation lead revision, system revision...). The study from Van Daele et al. 2021 [21] was not included in the analysis as it was a retrospective study. Based on the identified studies and the results from the EUnetHTA report [12], the overall strength of evidence for the safety of hypoglossal nerve stimulation (HGNS) compared with no treatment is considered to be low. Overall there is a lack of data on the durability of the device and long-term data on treatment effects. Further, complications and/or compliance in a general patient population that could be obtained through a longer follow-up are not available.
8	Transferability of the study population to the Austrian patient population (pp. 12 – 16)	We fully agree and think this point of critique is a result of misunderstandings and interpretations. As stated in the Discussion, Section *Internal and external validity*: The studies can be perceived as valid also to the Austrian context due to the study population and the study setting.
8.1	On the one hand, reference is made to 3 ongoing RCTs	Agreed, it is impossible to conclude on results that we do not know. The studies can change the evidence; only theoretical considerations were given in our report. In the report, we stated the following: "*Three*

	to which the HTA authors attribute little relevance prior to publication, without knowing the final results of the RCTs, as these will not be published until 2023/2024 (pp. 12)	*ongoing RCTs were identified with estimated completion dates within the next two years. Of which one study compares a one-month intervention with UAS against a control group with no intervention after one month (…)"* For this reason, the authors have proposed a re-evaluation after the studies have been published.
8.2	On the other hand, the authors of the 2nd HTA report criticise the fact that the current study populations are mostly male of Caucasian origin and thus not transferable to women or patients of non-Caucasian origin. (pp. 12 - 13)	Agreed; however, it was stated in our report as a general criticism of the studies that there is hardly any data on women and non-caucasians. We encourage and are keen to engage in a constructive scientific debate but would like to remind everybody that wild accusations based on interpretations of how authors may have meant a side sentence is not part of a rigorous scientific debate.
8.3	Prevalence by gender (p. 13)	Agreed, same as above.
8.4	Prevalence in relation to race (pp. 15 – 16)	Same as above. We never used the term race in our report and, hence, did also not highlight that HGNS would be applicable/ not be applicable to certain "racial groups" (politically correct: ethnic groups) as written in the point of critique. We question the notion of the importance of highlighting "racial" differences with regard to HGNS. Generally, we take a critical view of the term ''race'' in the field of medical research. It comes to our understanding that race information can be inconsistent and are often not very usable. Besides, race may also be a painful historic relict that may, at best, be an imperfect surrogate endpoint for other sociological variables (such as social determinants of health). We fully agree with John Ioannidis when saying that *"(…) just as the lens of science was used to establish a flawed premise of biological race-based differences, so should science now focus on illuminating that which is represented by race and become a trailblazer toward better health equity." [22]*

Abbreviations: AIHTA – Austrian Institute for Health Technology Assessment; HGNS- Hypoglossal nerve stimulation; HTA – Health Technology Assessment; OSA – obstructive sleep apnea; p. – page; pp. – pages; RCT – randomised controlled trail; SADEs - serious adverse product-related events; SAEs – serious adverse events.

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