# Stakeholderrückmeldungen zum Scoping Bericht “Sedativa»

## Juni 2021

Folgende Stakeholderverbände wurden zur Stellungnahme zum Scoping Bericht angeschrieben.

ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana
BSV - Bundesamt für Sozialversicherung, Invalidenversicherung
curafutura - Die innovativen Krankenversicherer
DVSP - Dachverband Schweizerischer Patientenstellen
FMH - Verbindung der Schweizer Ärztinnen und Ärzte
FRC - Fédération romande des consommateurs
GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren
H+ - Die Spitäler der Schweiz
Intergenerika - Swiss Generics and Biosimilars
Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz
Konsumentenforum
MTK - Medizinaltarif-Kommission
pharmaSuisse - Schweizerischer Apothekerverband
PUE - Preisüberwachung
SAMW - Schweizerische Akademie der Medizinischen Wissenschaften
santésuisse - Die Schweizer Krankenversicherer
SAPW - Schweizerische Akademie der Pharmazeutischen Wissenschaften
SBK - ASI - Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner
SFGG/SPSG - Schweizerische Fachgesellschaft für Geriatrie
SGAIM Schweiz. Gesellschaft allgemeine Innere Medizin
SGPMR - Schweizerische Gesellschaft für Palliative Medizin, Pflege und Begleitung
SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte
SKS - Stiftung für Konsumentenschutz
SPO - Patientenschutz
SUVA
SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen
Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC)
VIPS - Vereinigung Pharmafirmen in der Schweiz

**Folgende Stakeholder haben Stellungnahmen zum Scoping Bericht eingereicht:**

Curafutura, Interpharma, SGAIM Schweiz. Gesellschaft allgemeine Innere Medizin, Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC) ….

Stellungnahmen, welche nicht im vorgegebenen Feedbackformular eingingen, wurden sinngemäss ins Feedbackformularformat übertragen.

Formular A: Kommentare und Stellungnahmen der Stakeholder zum vorliegenden Scoping Bericht

## Allgemeines Kommentar

| Stakeholder | Stakeholder comment | Response | Responder |
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| curafutura | The scoping report was carried out lege artis. The question is clearly formulated, and the topic is current. The question arises as to what is to be achieved with the HTA, since it is to be done from the payer perspective.<br>For the ATC group N05BA there is already a point limitation imposed by the BAG (quantitative restriction). For the ATC group N05CF, the approval regulates the maximum duration of therapy (a maximum of 4 weeks or «An extension of the treatment should not be carried out without weighing the risks and benefits").<br>The costs of the preparations are not high, but there is a certain number of patients who take these preparations in the short and long term. Due to the low costs, the focus should be more on effectiveness, safety and legal, social, ethical and organizational issues rather than on costs, budget impact and cost-effectiveness. An important aspect here would be the issue of dependency (misuse, abuse) and follow-up costs from falls (fractures, etc.) | We agree with the SH that costs are not the most interesting aspect of the HTA. It's the side-effects and their consequences that are of true interest. However, an HTA addresses all HTA domains in an equal manner. One cannot focus more or less on one domain based on preference or disinterest.<br><br>Efficacy, safety, and legal, social, ethical, and organisational issues will be covered in the HTA report. In addition, the health economic model will model the costs and health consequences of drug dependency and car accidents and falls caused by sedative-hypnotic drug use. | iMTA |
| Interpharma | We thank you for the delivery of the above-mentioned scoping report and hereby take the opportunity to submit a timely statement. As an association of innovative drug manufacturers, Interpharma will not go into detail on the technical aspects of the scoping report, but rather concentrate on the overarching aspects of the procedure. HTA not suitable to investigate overprescription.<br><br>The chapter "policy question and context" mentions that Santésuisse proposed the topic. This is based on an observation that in the Netherlands the prescription of benzodiazepines has decreased after the health insurances no longer reimbursed them. This suggests an overprescription for this class of drugs. In our view, overprescription is a problem that HTA cannot fix. In addition, the selected studies go does not address this problem. If it is suspected that benzodiazepines are being prescribed too frequently in Switzerland, specific data on this question should be collected and evaluated. However, an HTA would be the wrong way to clarify and fix this problem.<br><br>Association of Research-Based Pharmaceutical Companies in Switzerland Substances that are not approved for chronic sleep disorders, in PICO table 1 on page 13 of the | Overprescription is indeed not an issue addressed by HTA.<br><br>The stakeholder is right, that some of the in the PICO listed drugs are not indicated for chronic sleep disorders.<br>The authors are aware of that and acknowledge this. Nonetheless, there is a solid argument to not change the study selection criteria, as proposed by the stakeholder.<br><br>This HTA report evaluates three drug categories N05BA (benzodiazepine derivatives), N05CD (benzodiazepine derivatives), and N05CF (Z-drugs/benzodiazepine related drugs). This list in | iMTA |

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| | scoping report, lists all substances of the three ATC categories N05BA, N05CD and N0CF examined. It is noticeable that a number of them, for example Lorazepam (Temesta) or Prazepam (Demetrin), are not even approved for the "chronic sleep disorder" indication examined. These active ingredients must not be part of an HTA, which examines the efficiency and effectiveness of the same active ingredient category for this indication.<br><br>Furthermore, by performing its supervisory tasks, the BAG can already ensure that health insurers only pay for these drugs within the approved indication. We thank you for considering our objections and suggestions and are available at any time for questions and additional explanations. | the PICO table contains all drugs that belong to those categories that are available in Switzerland.<br><br>In the HTA report the available evidence will first be reported by category. Subsequently, evidence pertaining to the specific drugs will be presented by subgroup analysis. This way, the evidence pertaining to the drugs that are not approved for chronic sleep disorders in Switzerland can easily be separated from the evidence pertaining to drugs that are approved for chronic sleep disorders. | |
| santésuisse | The report shows the question of the use of sleeping pills for use in chronic sleep problems. It is clearly structured. At the same time, certain information is only presented superficially, including information on the RCTs found and the drugs / substances (groups) addressed therein.<br>Certain framework conditions have to be worked out more clearly in order to be able to adequately address the actual question. | Detailed framework conditions are to be worked out in the HTA phase. | iMTA |
| SGAIM | The scoping report takes up all essential questions. | Thank you. | iMTA |
| SGSSC | The scoping report picks up on a topic that is important from our point of view. The evaluation of the long-term treatment of insomnia with medicinal methods is still an important research area in sleep medicine. In general, it should be noted that only a time-limited literature search was carried out for the report. This is one of the reasons why there are very few studies left that meet the evidence-based requirements and also only concern the so-called Z-drugs. In order to appreciate the entire field of hypnotics, one would also have to explicitly include studies on benzodiazepines, i.e. those that were carried out in earlier years before the year 2000. | In our search for recent systematic reviews/meta-analyses we used the search limit of 2010. Reviews will include studies conducted and published before 2010, covering a broad period. Our search for original up-to-date RCTs was extended to 2000, to cover more articles published. Existing systematic reviews in which RCTs were included on long-term use of sedative hypnotic-drugs, were used to determine the search periods. We checked all references of the systematic reviews that were selected after title/abstract screening and reported data on long term-use. In those systematic reviews, only one article published in 1999 appeared to be possibly of interest: a small RCT comparing CBT-I, CBT-I and BZD combined, BZD and placebo in insomnia patients and reported minimal results. This | Pallas |

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| | | confirms our decision to the search period for RCTs.<br>We want to highlight that we found studies on benzodiazepines within this publication period limit. However, non of those studies fulfilled our inclusion/exclusion criteria. For example, these studies were in people with depression/anxiety, or benzodiazepines were compared to another drugs (drug – drug comparison). | |

## Kommentar zum PICO

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| Curafutura | The scoping report focuses on the question and the PICO scheme as well as the methodology of the literature search. As a result, the report is much shorter and more concise than other scoping reports, which is very welcome. It should also be emphasized positively that the entire literature analysis was not already done in scoping.<br>The definition of patients (P) lacks a clear definition of insomnia according to ICD-10 or DSM-V. The examined patients should be restricted to the isolated insomnia, otherwise the differentiation from other clinical pictures that show an insomnia as a symptom is difficult and thus the informative value of an HTA would be limited. The periods of administration (more or less than a month) should also be defined more precisely.<br>The proposed HTA core questions would answer many different questions, which is why the effort involved will be correspondingly high. | The report indeed addresses primary insomnia that cannot be explained by other diseases. This was specified in the exclusion criteria in Table 3 and 4. But we will add 'primary' to the P in the PICO table for clarification. The new P in the PICO table will be: Adult patients with primary chronic insomnia disorder.<br><br>In addition, we will add the following to the study population in the inclusion/exclusion tables: Study with focus on a general population with chronic insomnia disorder (e.g., according to DSM-5, ICD-10, or ICSD-3) | Pallas |
| santésuisse | The research questions are basically understandable. For the implementation of a full HTA, however, some framework conditions have to be specified. This includes the boundary between short-term and long-term use, the definition of chronic sleep problems, etc.<br><br>In addition, the control group should be supplemented with pharmacological alternatives such as phytopharmaceuticals, melatonin, etc., which definitely play a role today, as is also mentioned in the report. | The mentioned framework conditions will be specified in the HTA phase.<br><br>Pharmacological alternatives are outside the scope of this HTA.<br><br>The clinical outcomes for the systematic review of efficacy, effectiveness and safety were already | iMTA |

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| | The clinical outcomes should also be further elaborated. Among other things, under the influence of daily activities after taking sleeping pills, further possible measuring points should be defined (e.g. reduced concentration, risk of falling, etc.) | specified and will not change in the HTA phase. However, additional clinical outcomes may be included in the health economic model. These will be further specified in the HTA phase. | |
| SGAIM | The research question is meaningful and relevant for practice. The use of a PICO makes sense. | Thank you. | iMTA |
| SGSSC | It should focus on chronic, non-organic insomnia in adults without psychiatric co-morbidity. Most patients who take benzodiazepines for long periods of time also have other problem areas.<br>Psychiatric co-morbidities such as anxiety disorders, affective disorders (especially depression), post-traumatic stress disorders and somatoform pain disorders play a major role. In this regard, the question needs to be sharpened.<br><br>A second point is the development of addiction to hypnotics. In the case of long-term treatment, especially with benzodiazepines, the risk of discontinuation must be compared with the risk of continuing therapy. Clinically, there are many patients who sleep well for many years with a hypnotic without increasing the dose. A withdrawal attempt can only generate the problems, with corresponding follow-up costs. The PICO approach seems okay to us. | The report addresses primary insomnia that cannot be explained by other diseases. This was specified in the exclusion criteria in Table 3 and 4. But we will add 'primary' to the P in the PICO table for clarification. The new P in the PICO table will be: Adult patients with primary chronic insomnia disorder.<br><br>In addition, we will add the following to the study population in the inclusion/exclusion tables: Study with focus on a general population with chronic insomnia disorder (e.g., according to DSM-5, ICD-10, or ICSD-3)<br><br>It will be explored whether addiction to sedative-hypnotic drugs can be taken into account in the health economic analyses in the HTA phase. Discontinuation is outside the scope for the current research objective, but we will model the impact of short-term use versus long-term use of sedative-hypnotic drugs. | Pallas |

## Kommentar zur Literatursuche

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| Curafutura | The literature search was carried out comprehensibly according to objective criteria and described in an understandable manner in the report. | Thank you. | Pallas |

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| santésuisse | Even if more and more overlaps are to be expected from the search in several databases, more than just two databases should be used for a literature search as part of a full HTA. Usually the databases Cochrane Library, Embase, GoogleScholar, PubMed and ClinibalTrials.gov are taken into account. It must also be checked whether the use of guidelines can provide further information on relevant literature and framework conditions (duration of a short-term use, etc.).<br><br>If possible and sensible, the various substances (groups) should be considered and worked out in a differentiated manner.<br><br>Furthermore, the three languages of Switzerland (D, I, F) should at least be taken into account in the research in order to map the regionality, especially when it comes to the question of ethical, social and legal aspects.<br><br>Do you think certain studies are missing?<br>Yes<br>The inclusion of guidelines but also non-randomized, comparative studies at least to sharpen the question should be examined. However, this also applies to substances (groups) where no RCTs are available and therefore fundamentally there is no evidence.<br><br>The approval studies of the various drugs should also be taken into account as an important basis. This also applies to studies that primarily show short-term use, which, however, could also provide important indications for inadequate use in long-term use.<br><br>In addition, the 9 RCTs listed seem to cover only a few different substances. This fact must be taken into account in order to obtain a meaningful HTA. In order to assess the aspect of safety, it must also be checked whether studies with the use of the substances over a short period should not be included. | Only peer-reviewed literature will be included in the systematic literature search. It was decided not to search in other databases, because in general there is much overlap between databases. The choice for the literature databases was discussed and agreed upon by the FOPH project team. During the full-text screening phase, reference lists of the included studies in the scoping report were checked to find any other studies that were not captured with our literature search. It was decided not to search in Cochrane Library as additional database, because RCTs on medication are sufficiently covered with the two databases PubMed (MEDLINE) and Embase.com. Additionally, the RCTs reported in Cochrane library are retrieved from PubMed and Embase. We disagree with the reviewer that Google Scholar is a valid peer-reviewed literature source for systematic reviews. It is not possible to search systematically with Google Scholar, because amongst others the search results are not necessarily reproducible. Clinicaltrials.gov is a database for privately and publicly funded clinical studies and not a source of peer-reviewed literature. Guidelines are covered with an additional grey literature search.<br><br>If possible, the outcomes will be stratified by sedative-hypnotic drugs.<br><br>The majority of the peer-reviewed articles (type of studies to be included in the systematic literature search) are published in English. Articles published in German and French are included (see inclusion and exclusion criteria table). Questions on ethical, social and legal aspects are part of the HTA, where regional variation might be taken into account. | Pallas iMTA |

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| | | See comment on inclusion of guidelines above.<br>In case no or only one RCT is found, an additional systematic literature search will be conducted for comparative non-randomised studies. Since nine RCTs are included with the systematic literature search for RCTs, it was decided not to proceed with the systematic literature search for comparative non-randomised studies.<br><br>Approval studies, if performed within our time-window and in line with our inclusion and exclusion criteria, will have been checked full text to see if they contained relevant information and are not excluded in advance.<br><br>Short-term use studies are only of interest when compared to a long-term use study. If not, short-term use studies are out of scope.<br><br>We are aware that only a few different substances are covered with the nine included RCTs. This means that we can only answer the research questions for the substances that were covered in the nine included RCTs. This will be taken into account as a limitation in the HTA report. | |
| SGSSC | Studies on benzodiazepines are also to be included here: Since these came onto the market in the 1960s, earlier studies, i.e. those before the year 2000, would also have to be included in the analysis (especially placebo-controlled or those with reference substances). The information on psychiatric co-morbidity must also be strictly observed, as well as the problem of addiction development, unless this is recorded under the side effects. It is also possible that there is not enough literature here so that one could alternatively rely on a consensus of expert opinions.<br>Comparative studies with other substances such as sleep-inducing antidepressants should also be integrated into the literature search with regard to the long-term drug treatment of primary, chronic insomnia. | We acknowledge that studies on benzodiazepines (BZD) are not included. However, reviews will include studies conducted and published before 2010. We checked all references of the systematic reviews that were selected after title/abstract screening and reported data on long term-use.<br>In those systematic reviews, only one article published in 1999 appeared to be possibly of interest: a small RCT comparing CBT-I, CBT-I and BZD combined, BZD and placebo in insomnia patients and reported minimal results. This confirms | Pallas |

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| | Missing any studies? yes<br>There are no previous studies on benzodiazepines (older than 2000) with the indication of sleep and sedation. | our decision to the search period for RCTs (i.e. 2000).<br>We want to highlight that we found studies on benzodiazepines within this publication period limit. However, none of those studies fulfilled our inclusion/exclusion criteria. For example, these studies were in people with depression/anxiety, or benzodiazepines were compared to another drugs.<br><br>Psychiatric co-morbidity is out of scope when it is not recorded as side-effect. In the systematic literature search only peer-reviewed studies are considered and expert opinions are out of scope.<br>In general, comparisons of BZD, BZD-derivates and Z-drugs with other substances is out of scope for the FOPH. | |

## Kommentar zur Analyse und Synthese

| Stakeholder | Stakeholder comment | Response | Responder |
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| Curafutura | It is to be welcomed that no content-related summary and analysis of the study results was made, as this should be part of the full HTA. However, in the Outlook chapter it is clearly described how the full HTA could be carried out and which questions still need to be clarified. The authors seem to have dealt intensively with the question and also with the Swiss context. | Thank you. | iMTA |
| santésuisse | Nine RCTs were found to assess efficacy and safety, among other things. As part of a full HTA, it can be expected that further studies will be found that are relevant to the question.<br>With the systematic literature search on cost-effectiveness, two studies on the long-term use of sedatives and hypnotics for the treatment of chronic sleep disorders were found. The studies identified provide insufficient evidence to assess the cost-effectiveness of the intervention in the Swiss context. We support the recommendation to develop a new model that reflects the situation in Switzerland. | Thank you for your support. | iMTA |

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| SGSSC | As already stated, the literature search falls short in our view, as it does not include older studies. In addition, psychiatric co-morbidities would have to be included in the analysis / synthesis as another important variable, otherwise the result will not reflect real needs. | In our search for recent systematic reviews/meta-analyses we used the search limit of 2010. Reviews will include studies conducted and published before 2010, covering a broad period. Our search for original up-to-date RCTs was extended to 2000, to cover more articles published.<br>Existing systematic reviews in which RCTs were included on long-term use of sedative hypnotic-drugs, were used to determine the search periods. We checked all references of the systematic reviews that were selected after title/abstract screening and reported data on long term-use.<br>In those systematic reviews, only one article published in 1999 appeared to be possibly of interest: a small RCT comparing CBT-I, CBT-I and BZD combined, BZD and placebo in insomnia patients and reported minimal results. This confirms our decision to the search period for RCTs.<br>We want to highlight that we found studies on benzodiazepines within this publication period limit. However, none of those studies fulfilled our inclusion/exclusion criteria. For example, these studies were in people with depression/anxiety, or benzodiazepines were compared to another drugs. | Pallas |

## Kommentar zur Durchführbarkeit eines HTA

| Stakeholder | Stakeholder comment | Response | Responder |
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| Curafutura | Based on the scoping report, how do you assess the feasibility of a full HTA?<br>Feasible<br>A full HTA seems to be theoretically feasible, but should focus on effectiveness, safety as well as legal, social, ethical and organizational aspects.<br>It would also be important to examine the subject of dependency related to the issue (misuse, abuse) and follow-up costs from falls. | Dependency will be taken into account in the health economic model when possible.<br><br>'Primary' will be added to the P in the PICO table for clarification. The new P in the PICO table will be: Adult patients with primary chronic insomnia disorder. | iMTA |

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| | In order to increase the informative value of an HTA, the examined clinical picture (insomnia) should be restricted to the isolated insomnia according to ICD-10 and the periods of administration should be defined more precisely. | In addition, we will add the following to the study population in the inclusion/exclusion tables: Study with focus on a general population with chronic insomnia disorder (e.g., according to DSM-5, ICD-10, or ICSD-3) | |
| santésuisse | Based on the scoping report, how do you assess the feasibility of a full HTA?<br>Feasible<br>On the basis of the information presented here, it can be assumed that a full HTA can be carried out in order to obtain answers to the questions formulated. On the basis of the information provided on the 9 RCTs on efficacy and safety, however, there remains a certain amount of uncertainty about the effective evidence that can be obtained from them. The differentiation between individual substances (groups) is also important. | The feasibility of conducting an HTA depends on the availability of evidence, not on the quality or certainty of the findings that are collected during the data searches. It is not excluded that the 9 RCTs will provide inconclusive findings, due to e.g. inconsistency between or poor quality of the studies, or insignificant effects. Differentiation between individual substances (or groups of substances) is outside the scope of our project. "Differentiation between individual substances address another research question, which is beyond the scope of this project." | |
| SGAIM | Based on the scoping report, how do you assess the feasibility of a full HTA?<br>Partly feasible<br>The data situation is extremely poor on the economic issues. For example, only one English and one Irish study that included economic parameters could be taken into account, whereby the Irish study does not contain any information on benzodiazepine consumption.<br>The report states that there is insufficient evidence on the "cost-effectiveness of long-term use of sedative-hypnotic drugs". Furthermore, there is a lack of information on the Swiss context. The application of a "de novo economic model" is recommended. The question arises for the SGAIM, how meaningful an HTA can be under these conditions. For this reason, we see the feasibility of the HTA only to a limited extent. In our opinion, only HTAs should be carried out that are based on valid data, in order to finally achieve a sufficient informative value. | We agree based on the literature search the data availability is limited. We will use published data from scientific literature as much as possible. But if certain data is not available, we will define assumptions based on expert opinion to populate the model. Extensive sensitivity analyses will be performed to explore the robustness of the results when these assumptions are varied. | iMTA |
| SGSSC | Based on the scoping report, how do you assess the feasibility of a full HTA? Feasible<br>The HTA takes into account important factors of economy, effectiveness and expediency. Social, ethical and demographic factors are taken into account. Comparisons are made with first-line treatments (CBT, CBTi; online CBTi) and placebo. However, there are no studies on comparative substances (e.g. sleep-regulating | Thank you. | iMTA |

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| | antidepressants). The literature research is carried out lege artis, whereby, as mentioned above, additional literature would also have to be included before the year 2000. Overall, the scoping report offers a well-founded, detailed and differentiated basis for carrying out the Health Technology Assessment (HTA). | | |