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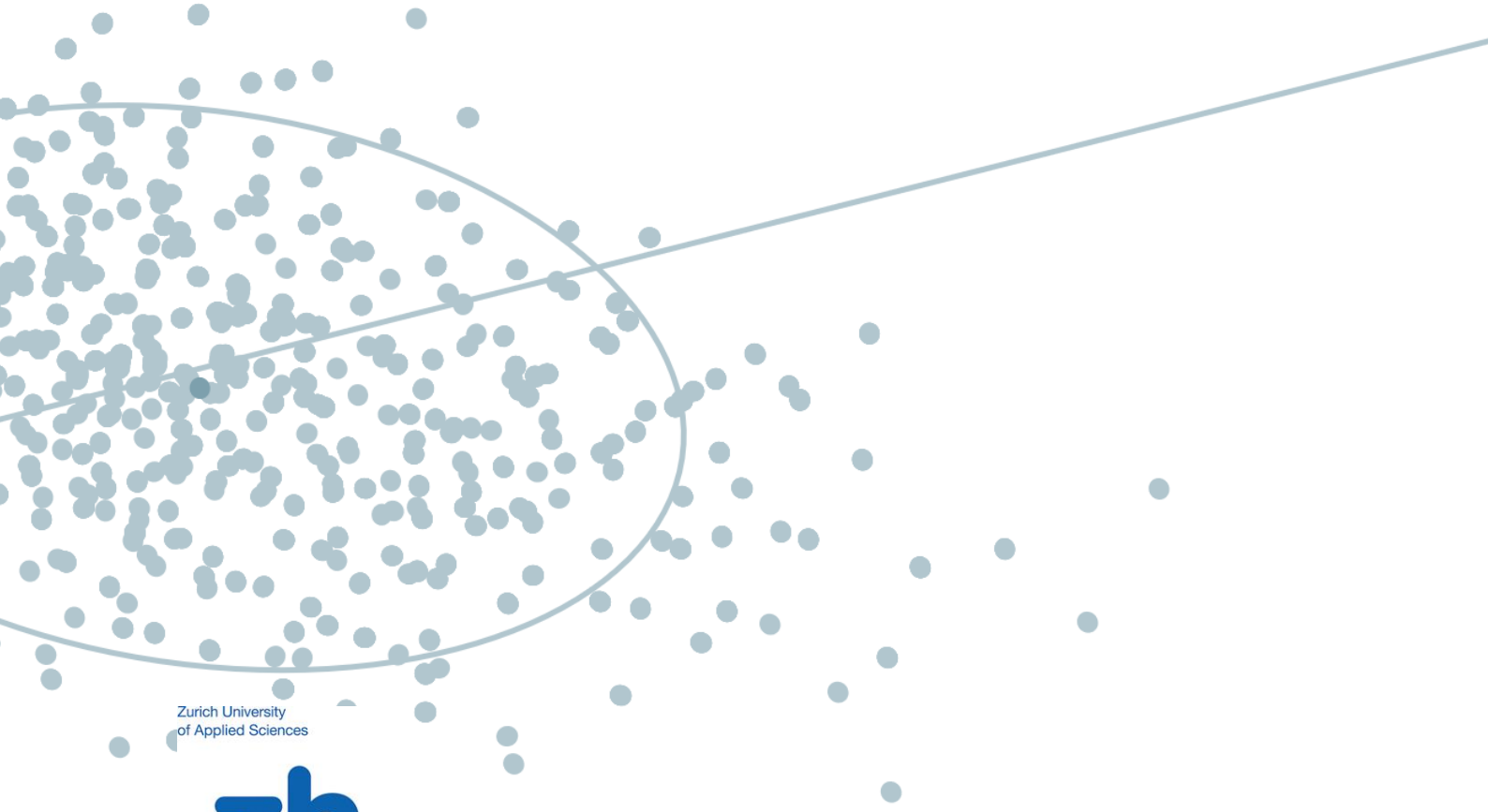
Health Technology Assessment (HTA)

HTA Protocol

Medicines containing valerian for treating symptoms of insomnia, mental stress and test anxiety

Version 05/06/2025



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Title	Medicines containing valerian for treating symptoms of insomnia, mental stress and test anxiety
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Technology	Medicines containing valerian extract, either alone or combined with lemon balm, hops, and/or other herbs (Sedonium®, Dormiplant®, Hova®, Redormin®, Relaxane®)
Date	05-06-2025

Conflict of Interest:

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Background: Valerian is a herbal remedy that has gained popularity in recent years as a sedative and hypnotic alternative to prescription drugs. However, evidence on its clinical effectiveness is inconsistent in the literature. In Switzerland, it is among the most recommended treatments for insomnia by pharmacies, along with relaxation therapy and other phytotherapies. Medicines containing valerian extract, either alone or combined with lemon balm, hops, and/or other herbal extracts are reimbursed by the Swiss mandatory health insurance for treating symptoms related to insomnia, mental stress or test anxiety. As part of the Swiss Federal Office of Public Health (FOPH) health technology assessment (HTA) program, an HTA report will be prepared based on this protocol to assess reimbursed medicines containing valerian. The findings will support evidence-based decision-making regarding the future reimbursement of these medicines by Swiss mandatory health insurance.

Objective: This protocol defines the population, intervention, comparator, and outcomes (PICO), as well as the key research questions and describes the methodology to conduct a systematic literature search, and extract, analyse and synthesise the data in the HTA report. Furthermore, a description of the planned budget impact analysis and the approach to address ethical, legal, social, and organisational issues related to the topic is provided.

Research questions: 1) What is the efficacy, effectiveness and safety of a treatment with medicines containing valerian (alone or in combination) compared to placebo, other herbal medicines, cognitive behavioural therapy, (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene), other medications, or no treatment in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety? 2) What is the cost-effectiveness of medicines containing valerian (alone or in combination) for treating symptoms of insomnia, mental stress or test anxiety? 3) What is the budget impact of Dormiplant®, Hova®, Redormin®, Relaxane®, Sedonium® for the currently reimbursed populations? 4) Are there ethical, legal, social or organisational issues related to the use of medicines containing valerian (alone or in combination) for treating symptoms of insomnia, mental stress or test anxiety?

Methods: Two systematic literature searches for evidence on efficacy, effectiveness, safety, and health economic outcomes will be conducted in Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE, PsycInfo, Web of Science, EconLit, International HTA Database, National Health Service Economic Evaluation Database, clinicaltrials.gov and the WHO International Clinical Trials registry Platform. Eligible studies are randomised controlled trials (RCTs), non-randomised controlled trials, controlled observational studies, health economic evaluations, budget impact analyses and other HTAs. The methodological quality of included studies will be critically appraised and the certainty of evidence for relevant efficacy, effectiveness and safety outcomes will be assessed by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Pairwise meta-analysis

will be performed for efficacy, effectiveness and safety outcomes when the amount of the evidence permits. In order to explore possible heterogeneity among pooled effect estimates and identify effect modifiers, subgroup analyses, as well as meta-regressions will be performed. Outcomes which cannot be summarised with pooled estimates will be analysed narratively by using the Synthesis Without Meta-analysis (SWiM) guideline. The results from the systematic review on health economic studies will be summarised narratively and relevant information will be used to construct a budget impact model. The budget impact for Switzerland will be estimated over the next 5 years and the analysis will be conducted from a health care payer perspective. Furthermore, a targeted search for evidence on ethical, legal, social and organisational aspects of medicines containing valerian will be conducted and findings will be summarised and discussed narratively. The “Hofmann catalogue” will be used to address specific ethical questions and a checklist designed for the Swiss legal system to address legal questions.

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Abbreviations and acronyms

BZRA	Benzodiazepine receptor agonists
CBT	Cognitive behavioural therapy
CBTI	Cognitive behavioural therapy for insomnia
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	Swiss Franc
CI	Confidence interval
DALYs	Disability-Adjusted Life Years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
ECG	Electrocardiograms
EEG	Electroencephalogram
e.g.	Exempli gratia (meaning “for example”)
ELSO	Ethical, legal, social and organisational
EUnetHTA	European network for Health Technology Assessment
EUR	Euro
ICER	Incremental Cost-Effectiveness Ratio
i.e.	Id est (meaning “in other words”)
FOPH	Federal Office of Public Health
GABA	Gamma-amino butyric acid
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HTA	Health Technology Assessment
LYs	Life Years
PSG	Polysomnography
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis

QALYs	Quality-Adjusted Life Years
RCT	Randomised controlled trial
RoB	Risk of Bias
SSRI	Selective serotonin reuptake inhibitor
SSSSC	Swiss Society for Sleep Research, Sleep Medicine and Chronobiology
SWiM	Synthesis Without Meta-analysis
USD	United States dollar
WASO	Wake After Sleep Onset
5HT	5-hydroxytryptophan

Objective of the HTA Protocol

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

1. Policy question and context

This HTA report addresses the following policy question:

Should the Swiss mandatory health insurance continue to reimburse medicines containing valerian extract or medicines in which valerian is combined with lemon balm, hops, and/or other herbal extracts?

The policy question addresses existing uncertainty around the technology's efficacy, appropriateness and cost-effectiveness and will be informed by answering the research questions of this health technology assessment (HTA) (See ***Chapter 5***).

Valerian is a herbal remedy that has gained popularity as a sedative and hypnotic alternative to other prescription drugs.[1] However, evidence on its clinical effectiveness is inconsistent in the literature.[1–5]

In Switzerland, it is among the most recommended treatments for insomnia by pharmacies, along with relaxation therapy and other phytotherapies, despite this approach being inconsistent with Swiss and European guidelines.[6–8] Medicines containing valerian extract, either alone or with lemon balm, hops, and/or other herbs are reimbursed by the Swiss mandatory health insurance to aid sleep and relief mild symptoms of mental stress and test anxiety.[9,10]

The expenditure[a] for valerian-based drugs in Switzerland has tripled, rising from CHF 7 million in 2014 to CHF 21 million in 2023.[11] The increasing expenditures and the uncertain clinical effectiveness of medicines containing valerian for treating symptoms related to insomnia, mental stress and test anxiety, have brought forward the need to re-evaluate these medicines.[7] The findings of this assessment will support evidence-based decision making regarding the future reimbursement of these medicines by the Swiss mandatory health insurance.

2. Medical background

2.1 Insomnia

Insomnia is the most common sleep problem affecting both the quality and quantity of sleep.[12,13] Its symptoms include difficulty in falling or staying asleep, waking up too early with problems returning to sleep, or feeling unrefreshed upon waking. These symptoms can manifest as acute, intermittent, or chronic and are often caused by stressors, medications, or underlying physical and mental health conditions like obesity, pain, anxiety, and depression.[13–16] Additionally, demographic and behavioural factors have been shown to influence the likelihood of experiencing insomnia

[a] These figures reflect only the costs covered by mandatory health insurance for medicines included in the list of pharmaceutical specialties ("Spezialitätenliste"), excluding out-of-pocket expenses and valerian tinctures reimbursed by the mandatory health insurance.

symptoms.[14,17] According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), insomnia becomes a disorder when the sleep difficulties occur at least 3 times per week and persist for at least three months.[13]

The diagnosis of insomnia in Switzerland involves a thorough medical history, covering aspects such as sleep habits, sleep environment, triggers, and chronobiological factors, as well as an external assessment of nocturnal abnormalities. A physical examination and laboratory tests are also performed. Additionally, psychiatric and somatic comorbidities, neurological symptoms and internal medicine-related complaints are assessed, along with a detailed review of the patient's medication and substance history. To support the diagnosis, various diagnostic tools are employed, including sleep questionnaires, sleep diaries, actigraphy, sleep electroencephalogram (EEG), and polysomnography (PSG).[7,8]

In Switzerland, the prevalence of insomnia is reported to be between 30% and 38% in the general population and among primary care patients, with 11% meeting the DSM-5 criteria for insomnia disorder.[16–19] Women and older adults are particularly prone to experiencing insomnia disorder, while there has been a significant increase in insomnia among individuals aged 15 to 39 since 1997.[8,16,18]

When insomnia becomes chronic (i.e., lasting more than 3 months), it can result in impaired daytime functioning and emotional distress, significantly reducing quality of life.[17,20] It also increases the risk of various other health conditions, contributing to substantial economic costs due to decreased work productivity, higher healthcare utilization, and a greater likelihood of accidents.[21–23] Chronic insomnia alone is estimated to cause an economic loss of approximately CHF 10 billion per year in Switzerland, which corresponds to 1.3% of the country's gross domestic product.[24] Despite this considerable impact, only 1% of the affected patients receive the recommended treatment.[18]

According to current guidelines from the Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SSSSC), the first-line treatment for insomnia and insomnia disorder involves adjusting sleep hygiene practices based on self-reported sleep habits. However, the recommended treatment approach is cognitive behavioural therapy for insomnia (CBTI).[8] This therapy typically involves 4-8 structured sessions and can be conducted individually or in groups. There are also internet-based, self-help, and brief versions, though internet-based programs have not yet been approved in Switzerland.[8] Randomised controlled trials (RCTs) show that CBTI is efficacious for insomnia, with or without comorbidities, and can also alleviate psychiatric symptoms.[25] If CBTI does not provide sufficient relief or is unavailable, pharmacotherapy can be considered.[7,8,14] For short-term use benzodiazepines and benzodiazepine receptor agonists (BZRA), also known as Z-drugs, are recommended. For longer-term treatment, sedative antidepressants are preferred, although they are not officially approved for insomnia in Switzerland.[8] The orexin receptor antagonist Daridorexant, approved in Switzerland since 2022 for chronic insomnia with considerable impairment of daytime activity, is also a preferred option. Antipsychotics are not recommended for treating

insomnia symptoms due to insufficient evidence and lack of approval in Switzerland. Antihistamines and melatonin are not recommended for the general population, although melatonin may be effective in children and adolescents. In Switzerland, melatonin is only approved for primary insomnia[b] in individuals aged 55 and older.

While CBTI has short-term efficacy comparable to hypnotics (e.g., benzodiazepines and BZRA), its long-term benefits are more sustainable, making it the preferred treatment for chronic insomnia, particularly given the risk of tolerance and dependence associated with benzodiazepines and BZRA.[8] Pharmacotherapy also carries risks such as confusion, falls, and daytime sleepiness, especially in elderly patients.[14] Phytotherapeutic treatments, such as medicines containing valerian extract, are widely accepted in Switzerland and serve as a low-threshold option.[8]

2.2 Mental stress and test anxiety

Mental stress is a natural response to life challenges and pressures. However, high levels of stress can negatively impact both physical and mental health and are associated, amongst others, with migraine, obesity, cardio vascular diseases and depression.[26–28]

Test anxiety, also known as exam anxiety, exam stress, or test stress, is a specific type of anxiety characterised by worry or fear in evaluative situations, such as exams.[29,30] Anxiety is characterised by symptoms that can manifest physically (e.g., increased heart rate, sweating, trembling), cognitively (e.g., excessive worrying, difficulty concentrating, feeling of fear or nervousness), and behaviourally (e.g., avoidance of situations) and that can vary in severity.[31] Studies suggest that 15% to 22% of students experience high levels of test anxiety.[29,30] The consequences of test anxiety can extend beyond the classroom and are correlated with poor health behaviours, including dysregulated sleep patterns and poor sleep quality.[32]

Anxiety disorders are among the most common mental health issues worldwide, affecting approximately 4% of the global population.[33] Prevalence rates vary by region, with higher rates observed in high-income countries, and have been rising significantly over the past decades.[33] In Switzerland, as of 2022, about 7.5% of men and 11.9% of women reported experiencing anxiety disorders within the previous year.[34] Anxiety symptoms are more common among women and younger individuals.[34,35]

According to Global Burden of Disease Study 2010 mental disorders were responsible for 18.9% of all years lived with a disability. Conditions like depression and anxiety contribute substantially to the world's disease burden and therefore place significant strain on the health care system.[36] A major portion of the costs associated with mental health issues, including anxiety, arise from lost productivity and informal care.[37]

Exercise, meditation and mindfulness have been proposed to help alleviate mental stress, and in students, interventions such as cognitive behavioural therapy and meditation have been shown to

[b] Primary insomnia is defined as not occurring in the context of another mental illness.[8]

reduce stress, anxiety and depression.[26,27,38,39] According to current Swiss guidelines on anxiety disorders, which are based on the German S3 guidelines developed by several psychiatric societies, both pharmacotherapy and psychotherapy can be used as first- or second-line treatments of different symptoms, either individually or in combination.[40,41] The choice of approach depends on the symptoms, its severity, the required time commitment, the availability of therapies, any costs incurred by the patient, individual preferences, and the presence of comorbid mental conditions.[40] Pharmacological and psychotherapeutic measures are viewed as complementary and mutually reinforcing methods that can be combined and tailored to the specific needs. A reassessment should take place if there is no response to therapy within 4 to 6 weeks. In cases where patients do not respond to prescribed medication, factors such as correct diagnosis, adherence, and sufficient dosage must be reassessed.[40] Pharmacotherapy should generally continue for 6-12 months after remission, and medications should be tapered off gradually to avoid withdrawal symptoms. Newer antidepressants are preferred for mid- and long-term management due to their lower risk of side effects, while benzodiazepines may be used briefly (max. 3-4 weeks) for acute symptoms. The Swiss Society for Psychiatry and Psychotherapy generally recognizes the following evidence-based psychotherapeutic methods: cognitive behavioural therapy (CBT), psychoanalytical oriented therapy, and systemic therapy.[40] Pharmacotherapy and psychotherapy may be complemented by additional interventions, such as occupational therapy, relaxation techniques, physical activity, psychoeducation, self-help groups, and family involvement. However, there is limited evidence from RCTs to confirm their efficacy.[40]

3. Technology

Valerian is a herbal remedy used as a sedative and hypnotic for treating symptoms related to insomnia, mental stress and test anxiety.[1] According to the patient information for approved valerian-containing medicines in Switzerland, the indications include symptoms such as difficulty falling asleep, staying asleep, poor sleep quality, as well as nervousness, tension, agitation and test anxiety (***Table 1***).[42]

Table 1: Indications of reimbursed drugs in Switzerland

Reimbursed drug	Indication	Ingredients
Dormiplant®	Restlessness, nervousness and difficulty falling asleep	Valerian root and lemon balm
Hova®	Nervous sleep disorders, nervousness, agitation/ restlessness	Valerian root and hop cone
Redormin®	Difficulty falling asleep, sleep disorders and restless sleep	Valerian root and hop cone
Relaxane®	Nervousness, states of tension and restlessness, test anxiety. These complaints can manifest themselves in the following symptoms, among others: cramp-like gastrointestinal complaints,	Valerian root, butterbur root, passionflower and lemon balm leaf

	increased irritability, occasional difficulty falling asleep and staying asleep.	
Sedonium®	Difficulty falling asleep and staying asleep as well as restless sleep	Valerian root

Source: Compedium[42–45]

Valerian's mode of action is not fully understood but may involve interactions with gamma-amino butyric acid (GABA) and 5-hydroxytryptophan (5HT) receptors.[46] Extracted from the roots of the Valeriana officinalis plant, valerian-containing medicines are available in various forms, including capsules, tablets, teas, and extracts.[2,47]

In Switzerland, valerian-containing medicines are widely used as hypnotics or sedatives and are available through pharmacies.[6,42] These medicines are available without a prescription. However, a prescription is required for reimbursement under the mandatory health insurance.

The specific dosage of valerian varies depending on the form and the specific product used.[10] Valerian products may contain varying concentrations of the active ingredient and may be combined with other herbal remedies, such as lemon balm, hops, butterbur, or passionflower.[2,47] While valerian is generally considered to have a low risk of harm, it may cause side effects, particularly in combination with certain medications. For instance, taking valerian with sedatives can lead to increased sedation.[48] Additionally, individuals should be aware of rare but possible side effects, such as allergic reactions and gastrointestinal discomfort. Liver disorders might also occur, though these are primarily associated with the use of butterbur extract.[42–45] The safety of valerian in pregnancy and breastfeeding has not been established, and it may cause side effects such as dizziness, headache, and gastrointestinal disturbances.[2,47]

Medicines containing valerian extract, either alone or in combination with lemon balm, hops, and/or other herbs, are reimbursed by Switzerland's mandatory health insurance for the treatment of symptoms related to insomnia, metal stress or test anxiety. Notably, a formal diagnosis of any of the conditions is not required for prescribing these medicines and it can also be prescribed for mild symptoms. The reimbursed products are Dormiplant®, Hova®, Redormin®, Relaxane ® and Sedonium®. All but Sedonium® contain valerian combined with another herb, such as lemon balm, hops, butterbur or passionflower.[10]

4. Population, Intervention, Comparator, Outcome (PICO)

PICO provides a structured framework for evidence-based research by defining the main components of an HTA research question. ***Table 2*** and ***Table 3*** present the PICOs regarding insomnia, ***Table 4*** the PICO regarding mental stress, and ***Table 5*** presents the PICO regarding test anxiety. The PICOs were defined in consultation with Swiss clinical experts in psychiatry and neurology, as well as phytotherapy experts.

Table 2: PICO 1 Patients with symptoms of insomnia treated with medicines containing valerian extract alone

P:	Patients (≥ 6 years) with symptoms[c] of insomnia
I:	Medicines containing valerian extract alone
C:	C-1 Placebo C-2 Lifestyle adaptation C-3 Improvement of sleep hygiene C-4 Other herbal medicines C-5 Cognitive behaviour therapy C-6 Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), or sedative antidepressants) C-7 No treatment
O:	**Efficacy/effectiveness:** • latency time in minutes until getting to sleep • number of nocturnal awakenings • wakefulness after sleep onset (WASO) • wake duration • sleep duration • objective sleep quality • subjective sleep quality • feeling of waking up refreshed • daytime sleepiness • quality of life **Safety**: • adverse events (total and by specific events, such as allergic reactions, and gas-trointestinal problems) • serious adverse events • discontinuation due to intervention **Economic**: • total and incremental costs, total and incremental QALYs and effects, and ICER. • budget impact

[c] Insomnia symptoms such as difficulty falling or staying asleep, and unsatisfying sleep.

Table 3: PICO 2 Patients with symptoms of insomnia treated with medicines containing valerian extract combined with lemon balm or hops

P:	Patients (≥ 6 years) with symptoms[d] of insomnia
I:	Medicines containing valerian extract in combination with lemon balm or hops
C:	C-1 Placebo C-2 Lifestyle adaptation C-3 Improvement of sleep hygiene C-4 Other herbal medicines C-5 Cognitive behaviour therapy C-6 Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), or sedative antidepressants) C-7 No treatment
O:	**Efficacy/effectiveness**: • latency time in minutes until getting to sleep • number of nocturnal awakenings • wakefulness after sleep onset (WASO) • wake duration • sleep duration • objective sleep quality • subjective sleep quality • feeling of waking up refreshed • daytime sleepiness • quality of life **Safety**: • adverse events (total and by specific events, such as allergic reactions and gas-trointestinal problems) • serious adverse events • discontinuation due to intervention **Economic**: • total and incremental costs, total and incremental QALYs and effects, and ICER. • budget impact

[d] Insomnia symptoms such as difficulty falling or staying asleep, and unsatisfying sleep.

Table 4: PICO 3 Patients with symptoms of mental stress treated with medicines containing valerian extract combined with lemon balm or hops

P:	Patients (≥ 6 years) with symptoms of mental stress
I:	Medicines containing valerian extract in combination with lemon balm or hops
C:	C-1 Placebo C-2 Other herbal medicines C-3 Cognitive behaviour therapy C-4 Medication (e.g., selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, or benzodiazepines) C-5 No treatment
O:	**Efficacy/effectiveness:** • change in anxiety symptoms (e.g., Hamilton Anxiety Scale (HAM-A) and other anxiety symptom scales) • quality of life **Safety**: • adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) • serious adverse events • discontinuation due to intervention **Economic**: • total and incremental costs, total and incremental QALYs and effects, and ICER. • budget impact

Table 5: PICO 4 Patients with symptoms of test anxiety treated with medicines containing valerian extract combined with lemon balm, passionflower and butterbur

P:	Patients (≥ 6 years) with symptoms of test anxiety
I:	Medicines containing valerian extract in combination with lemon balm, passionflower and butterbur
C:	C-1 Placebo C-2 Other herbal medicines C-3 Cognitive behaviour therapy C-4 Medication (e.g., selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, or benzodiazepines) C-5 No treatment
O:	**Efficacy/effectiveness:** • change in test anxiety symptoms (e.g., Hamilton Anxiety Scale (HAM-A) and other anxiety symptom scales) • quality of life **Safety**: • adverse events (total and by specific events, such as allergic reactions and gastrointestinal problems) • serious adverse events • discontinuation due to intervention **Economic**: • total and incremental costs, total and incremental QALYs and effects, and ICER. • budget impact

5. HTA research questions

The evaluated technology are medicines containing valerian extract, either alone or combined with lemon balm, hops, and/or other herbal extracts. For the evaluation of this health technology the following research questions, covering central HTA domains, as designated by the European network for HTA (EUnetHTA) Core Model (clinical effectiveness, safety, cost-effectiveness, budget impact, ethical, legal, social, and organisational (ELSO) aspects), are addressed. Research questions 1 and 2 evaluate the efficacy, effectiveness and safety of these medicines and research questions 3 and 4 evaluate the cost-effectiveness and budget impact. Research question 5 examines the ethical, legal, social and organisational issues related to the use of medicines containing valerian.

1. Are medicines containing valerian (alone or in combination) efficacious or effective compared to placebo, other herbal medicines, CBT, other medications or no treatment (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene) in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety?
2. Are medicines containing valerian (alone or in combination) safe compared to placebo, other herbal medicines, CBT, other medications, or no treatment (for symptoms of insomnia: also compared to lifestyle adaptation or improvement of sleep hygiene) in patients ≥ 6 years with symptoms of insomnia, mental stress or test anxiety?
3. What is the cost-effectiveness of medicines containing valerian (alone or in combination)?
4. What is the budget impact of Dormiplant®, Hova®, Redormin®, Relaxane®, Sedonium® for the currently reimbursed populations?
5. Are there ethical, legal, social or organisational issues related to the use of medicines containing valerian (alone or in combination) for treating symptoms of insomnia, mental stress or test anxiety?

6. Methodology

A systematic review will be conducted for the clinical evaluation and a separate systematic review for the economic evaluation. The methodology of both systematic reviews of this HTA has been developed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[49] and follows the reporting guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[50] Additionally, selective reviews will be conducted to assess the ELSO domains. Clinical outcomes for insomnia, mental stress and test anxiety will be analysed independently to ensure specificity and relevance.

6.1 Clinical evidence

6.1.1 Databases and search strategy

A systematic literature review of RCTs, non-randomised controlled trials and controlled observational studies will be conducted. The search strategy has been developed based on the PICO framework (***Chapter 4***) in collaboration with a medical librarian, following current best practice guidelines and taking the European Union herbal monographs on Valeriana officinalis L., radix and Humulus lupulus L., flos and on Valeriana officinalis L., radix into account.[49,51,52] Several relevant systematic reviews, meta-analyses and network meta-analyses studies were also considered when building the search strategy and were also used to validate its quality.[1–5,53–62] The systematic literature search will be conducted using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE, PsycInfo and Web of Science. Additionally, searches will be conducted in clinicaltrials.gov and the WHO International Clinical Trials Registry

to gain insights into planned or ongoing RCTs. The search strategy focuses only on the intervention component of PICO, while population, comparators and outcomes are not specified to avoid undue narrowing of the search results. Search limits are applied to capture only controlled clinical studies conducted in humans. Eligible study designs include RCTs, non-randomised controlled studies, observational studies with a control group (including longitudinal and retrospective designs, post marketing surveillance studies, and pragmatic trials). Studies on infants and conference abstracts will be excluded. The detailed search strategy in each database is outlined in ***Appendix 9.1***. All studies will be imported to CADIMA for study selection.

In addition to controlled studies, uncontrolled observational studies will be identified through published systematic literature reviews and monographs.

6.1.2 Study selection

The inclusion and exclusion criteria have been defined according to the PICO framework and are presented in ***Table 6***. All relevant outcomes defined in the PICOs will be considered. Although valerian-containing medicines in Switzerland are specifically indicated for symptoms related to mental stress or test anxiety (PICO 3 and 4), the literature search will initially include a broader population (anxiety in general) to optimize the pool of evidence, in case little evidence for the subpopulation is available. There will be no restrictions on the country, setting, sample size or publication period. The study design for the systematic literature review is restricted to RCT, non-randomised controlled trials and controlled observational studies. The publication language must be English, French, German, or Italian. Studies are eligible if they provide results for at least one outcome of interest. If relevant additional criteria emerge during the study selection, the inclusion and exclusion criteria will be adjusted in agreement with the Federal Office of Public Health (FOPH).

Table 6: Inclusion and exclusion criteria for clinical evidence

	Inclusion	Exclusion
Population	Human patients (≥ 6 years) with symptoms of insomnia, mental stress or test anxiety/anxiety	Animal studies, patients with symptoms not related to insomnia, mental stress or test anxiety/anxiety or patients below 6 years of age
Intervention	Medicines containing valerian extract alone, and medicines in which valerian is combined with either: 1) Lemon balm 2) Hops 3) Lemon balm, butterbur and passionflower	Any other intervention including medicines combined with non-herbal medication
Comparator	• Placebo • Lifestyle adaptation • Improvement of sleep hygiene • Other herbal medicines • Cognitive behaviour therapy • Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), sedative antidepressants, selective serotonin reuptake inhibitors or tricyclic antidepressants)) • No treatment Only comparators approved for use in Switzerland will be considered.	Any other comparator or comparators not approved for use in Switzerland

Outcomes	Efficacy, effectiveness and safety outcomes mentioned in Chapter 4	No efficacy, effectiveness or safety outcomes Outcomes only on pharmacokinetics or pharmacodynamics
Study design	RCT, non-randomised controlled trials or controlled observational studies (i.e., real world evidence)	Any other study design
Language	English, French, German or Italian	—
Country	No restrictions	—
Setting	No restrictions	—
Publication period	No restrictions	—
Publication status	Published in a peer-reviewed journal with full-text or essential content available	Published as a book, conference abstract, or journal article without full-text or essential content available

Abbreviation
RCT: Randomised Controlled Trial

In the first step, references will be screened by title and abstract by 2 reviewers independently using the inclusion/exclusion criteria. In the second step, full texts of retained studies will be reviewed independently by 2 reviewers. Disagreements will be resolved by consensus or by consulting a third reviewer. Prior training sessions will be held to increase consistency between reviewers. A PRISMA flow diagram will be created to illustrate study selection results, including the primary reasons for exclusion.

6.1.3 Data extraction, analysis and synthesis

6.1.3.1 Data extraction

Relevant data from included studies will be extracted by a single reviewer using REDCap, which will be pilot-tested with selected studies retained after full-text screening. A second reviewer will check the data against the original publication. Disagreements will be resolved by consensus, with a third reviewer consulted if needed. To ensure consistency, prior training sessions will be conducted. The REDCap data extraction form will include the following information (for outcomes on study arm level):

– Study characteristics: first author, title, country, publication year, setting, study period, length of follow-up, and source of funding.

– Population: age and sex, diagnosis, symptoms, sample size, number of randomised persons per study arm, comorbidities.

– Intervention: valerian drug, administration regimen, dosage, herbal preparation, timing after symptom onset and timing in relation to CBT, frequency, treatment duration.

– Comparator: exact comparator, administration regimen, dosage, timing after symptom onset, frequency, treatment duration.

– Outcomes: effect sizes and summary measures of clinical efficacy, effectiveness and safety outcomes mentioned in ***Chapter 4*** *(incl. method of assessment of adverse events)*.
– Quality Assessment: Information relevant to assess the quality of studies (i.e., information to perform the Risk of Bias (RoB), and Grading of Recommendations Assessment, Development and Evaluation (GRADE)).
– Additional Comments: Study limitations or issues not identifiable from other extracted data.

Details of ongoing or stopped RCTs identified in clinical trial registries will be extracted and summarized in a table. This table will include information on trial status, country, study period, population, intervention, comparator, outcomes, and estimated completion date.

6.1.3.2 Assessment of quality of evidence

The methodological quality of included RCTs will be critically appraised according to the Cochrane Risk of Bias 2 tool for randomised trials (RoB 2).[63,64] Non-randomised and observational studies will be appraised according to the Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.[65] Assessments will be performed in duplicate, and inconsistencies will be resolved by consensus or by consulting a third reviewer. The influence of studies with small sample size will be estimated using Egger's test of funnel plots.[49,67–70]

To obtain an overall rating of confidence in the estimates of effects, the GRADE approach will be applied, and the certainty of evidence for relevant outcomes will be rated in duplicate.[71] Inconsistencies will be resolved by consensus or by consulting a third reviewer. The GRADE summary of findings table will be produced for both population groups using the online tool.[72]

6.1.3.3 Data analysis and synthesis

The included studies will be presented separately for insomnia, mental stress and test anxiety in a table with information on study characteristics and relevant outcomes. RoB figures and a GRADE summary table will also be provided (See ***Chapter 6.1.3.2***).

Before conducting pairwise meta-analyses, clinical and methodological heterogeneity among included studies will be assessed by evaluating whether participants, interventions, comparisons and outcomes are judged to be sufficient similar to ensure that pooling estimates is methodologically appropriate (i.e., validated vs. not-validated instruments). Separate pairwise meta-analysis will be conducted for each outcome and each comparator to pool the estimated effects from the included studies with sufficient data for outcomes reported by at least 2 studies. When possible, forest plots will be presented. Additionally, cumulative meta-analysis will be performed to observe how the pooled estimate evolves over time and assess the evidence evolution. Pairwise meta-analyses will be conducted using the *metafor* package in R.[73] Heterogeneity will be addressed by employing a random-effects model with the restricted maximum likelihood method following the guidance of the Cochrane Handbook.[49] Continuous data will be pooled using weighted mean differences or standardised mean differences, while binary outcomes will be analysed using relative risks as the effect

measure.[49] If zero-event studies occur a continuity correction of 0.1 will be added. Sensitivity analyses with a continuity correction of 0.5 and 0.001 will be included. Uncertainty will be expressed with 95% confidence intervals. If enough studies are available the prediction interval will be assessed to consider heterogeneity.[74] In case pairwise meta-analyses are not possible, the evidence will be described narratively using the Synthesis Without Meta-analysis (SWiM) guideline.[75]

Subgroup and meta-regression analyses will be performed if appropriate to explore possible heterogeneity among pooled effect estimates and identify effect modifiers. The following subgroup analyses will be considered:

- Age groups (children 6-11 years, adolescents 12-17 years, adults 18-64 years, elderly ≥65 years)
- Sex
- Comorbidities
- Setting (e.g., community, inpatient, long-term care)
- Symptom definition and diagnosis
- Medication in the comparator arm (antidepressants, benzodiazepines)
- Administration regimen
- Dosage
- Valerian products reimbursed in Switzerland
- Herbal preparation (e.g., hydroalcoholic extracts, aqueous extracts, unspecified solvents, herbal substance)

The uncontrolled observational studies identified through published systematic literature reviews and monographs will be summarized narratively.

6.2 Economic evidence

The results from the systematic review of health economic studies will provide an overview of the existing knowledge on the health economic aspects of using medicines containing valerian (either alone or in combination). Relevant information from the included studies may also contribute to the development of the budget impact model.

6.2.1 Databases and search strategy

The search strategy for economic evaluations and budget impact analyses has been developed based on the PICO framework (***Chapter 4***) in collaboration with a medical librarian, following current best practice guidelines.[76–78] The systematic literature search will be conducted in the following databases: MEDLINE, Embase, the American Economic Association's electronic database EconLit, the International Network of Agencies for Health Technology Assessment (INAHTA) database,

and the National Health Service Economic Evaluation Database (NHS EED). The search strategy focuses on PICO's intervention and outcome component, while population and comparators are not specified to avoid undue narrowing of the search results. Search limits are applied to exclude animal studies, conference abstracts, and studies exclusively focusing on infants. The detailed search strategy in each database is outlined in ***Appendix 9.2***. All studies will be imported to CA-DIMA for study selection.

6.2.2 Study selection

The inclusion and exclusion criteria have been defined according to the PICO framework and are presented in ***Table 7***. Although valerian-containing medicines in Switzerland are specifically indicated for symptoms related to mental stress or test anxiety (PICO 3 and 4), the literature search will initially include a broader population (anxiety in general) to optimize the pool of evidence, in case little evidence for the subpopulation is available. There will be no restrictions on the country, setting, sample size or publication period. The publication language must be English, French, German, or Italian. Studies will be included if they fall under the category of original health economic evaluation, budget impact analysis or HTA of medicines containing valerian (alone or in combination).

Table 7: Inclusion and exclusion criteria for economic evidence

	Inclusion	Exclusion
Population	Human patients (≥ 6 years) with symptoms of insomnia, mental stress or test anxiety/anxiety	Animal studies or patients with symptoms not related to insomnia, mental stress or test anxiety/anxiety or patients below 6 years of age
Intervention	Medicines containing valerian extract alone, and medicines in which valerian is combined with either: 1) Lemon balm 2) Hops 3) Lemon balm, butterbur and passionflower	Any other intervention including medicines combined with non-herbal medication
Comparator	• Placebo • Lifestyle adaptation • Improvement of sleep hygiene • Other herbal medicines • Cognitive behaviour therapy • Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), sedative antidepressants, selective serotonin reuptake inhibitors or tricyclic antidepressants) • No treatment Only comparators approved for use in Switzerland will be considered.	Any other comparator or comparators not approved for use in Switzerland
Outcomes	Total and incremental costs, total and incremental QALYs and effects, ICER, budget impact	Patient satisfaction, biological or surrogate outcomes, narrative or qualitative outcomes.
Study design	HTAs, health economic evaluations, including within-trial or model-based cost-effectiveness, -utility, -benefit, -	Not health economic evaluation or budget impact analysis, for example cost-of-illness and resource use studies

	minimization, -comparison and budget impact analyses	
Language	English, French, German or Italian	—
Country	No restrictions	—
Setting	No restrictions	—
Publication period	No restrictions	—
Publication status	Published in a peer-reviewed journal or as HTA report with full-text or essential content available	Published as a book, conference abstract, or journal article without full-text or essential content available

Abbreviation
HTA: health technology assessment

All retrieved articles will be screened in duplicate by 2 independent researchers, similar to the systematic approach described in ***Chapter 6.1.2***. Prior training sessions will be held to increase consistency between reviewers. A PRISMA flow diagram will be created to illustrate study selection results, including the primary reasons for exclusion.

6.2.3 Data extraction, analysis and synthesis

Relevant data from included studies will be extracted by a single reviewer using REDCap. A second reviewer will check the data against the original publication. Disagreements will be resolved by consensus, with a third reviewer consulted if needed. To ensure consistency, prior training sessions will be conducted. The REDCap data extraction form will include the following information:

- Study characteristics: first author, title, country, publication year, healthcare setting, source of funding, study design, model type, perspective, time horizon, and discount rates used for costs and outcomes.
- Population: age, sex, diagnosis/symptoms, sample size, comorbidities.
- Intervention: type of valerian medicine, administration regimen, dosage, herbal preparation, administration regimen, treatment duration.
- Comparator: concrete comparator, administration regimen, treatment duration.
- Outcomes: costs of intervention and comparators, incremental costs, effectiveness in terms of life years (LYs), quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) of intervention and comparator, incremental effectiveness, incremental cost-effectiveness ratio (ICER), incremental net benefit, as well as measures of dispersion (e.g., standard deviation, standard error and 95% CI) and uncertainty (range reported by sensitivity analysis). Where applicable, data from the cost-effectiveness plane will be extracted using the WebPlotDigitizer software V.4.5

6.2.3.1 Assessment of reporting quality

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist will be used to assess to what extent the included studies meet the reporting standards for peer-

reviewed publication purposes.[79] A narrative assessment of study limitations will summarise any residual issues of included studies which could not be addressed in the quality assessment.

6.2.3.2 Data synthesis

The included studies will be presented separately for insomnia, mental stress and test anxiety in a table with information on study characteristics. Key findings for each PICO will also be presented in tabular or graphical form.

6.2.4 Cost-effectiveness analysis

The cost-effectiveness analysis in this report will present the best available published data from cost-effectiveness analyses retrieved from the scientific literature.

The findings will serve to give an overview of conducted analyses of medicines containing valerian (either alone or in combination). The findings will be summarised in narrative form, and the quality of these studies will be discussed. No transferability assessment will be conducted.

6.2.5 Budget impact analysis

A detailed description of the methodology of the budget impact analysis will be provided in the final HTA report. The main components are described here.

The budget impact aims to provide supporting information for a reimbursement decision in the form of an alternative scenario of what would happen in case that medicines containing valerian (alone or in combination), would continue to be available but no longer reimbursed by the compulsory health insurance. Notably, the impact on different subgroups will be examined based on the available alternative medications, their health impacts (if applicable), and the associated costs.

Health care claims data from a Swiss health insurance company will be analysed to estimate the current consumptions of reimbursed products, identify the current intervention mix and utilisation patterns, and calculate symptom/condition-related costs. Information on treatment pathways, combined with Swiss treatment guidelines, and clinical expert opinion will help determine the relevant treatment alternatives and assess the potential substitution effects if valerian-containing medicines are removed from the list of reimbursed medication. Intervention and comparator costs will be estimated using health insurance data, published literature, list of pharmaceutical specialties (Spezialitätenliste) and Swiss healthcare tariffs.[10]

Clinical evidence will be considered, including cases where the efficacy of valerian is found to be comparable to that of a placebo. In this case, if valerian is no longer reimbursed and some patients receive no alternative treatment for their symptoms, it will be assumed that their health outcomes may deteriorate due to the loss of valerian's placebo-like effect, which will be reflected in increased symptom-related costs. Potential harms from the use of valerian-containing medicines will also be considered.

Parameter uncertainty and structural uncertainty will be explored through deterministic and probabilistic sensitivity analyses. Clinical experts will be consulted to establish the face validity of the proposed model and associated assumptions.

6.2.5.1 Population

Patients (≥ 6 years) with symptoms of insomnia, mental stress, or test anxiety.

6.2.5.2 Intervention(s)

Medicines containing valerian extract alone and medicines in which valerian is combined with either: lemon balm, hops or lemon balm together with butterbur and passionflower

6.2.5.3 Comparator(s) (potential)

- Lifestyle adaptation
- Improvement of sleep hygiene
- Other herbal medicines
- Cognitive behaviour therapy
- Medication (e.g., benzodiazepines, benzodiazepine receptor agonists (Z-drugs), sedative antidepressants, selective serotonin reuptake inhibitors or tricyclic antidepressants)
- No treatment

6.2.5.4 Perspective

The healthcare payer perspective will be applied. Only direct medical costs related to treatment and management of symptoms will be considered.

6.2.5.5 Time horizon

The time horizon will be 5 years in accordance with best practice guidelines.[80]

6.2.5.6 Discount rate

No discount rate will be applied to reflect the budget impact at each point in time, in accordance with best practice guidelines.[80]

6.3 Evidence on ethical, legal, social, and organisational aspects

6.3.1 Databases and search strategy

To assess the ELSO aspects, pertinent issues will be identified from the studies included in the clinical and economic evaluations. Additionally, targeted, selective searches in MEDLINE, Swisslex, Legalis and relevant websites (of health authorities, research groups and non-governmental organisations) will be performed to gather relevant information. National and international regulations, guidelines and recommendations as well as judgements, reports and (specialist and grey) literature related to these domains will be identified and reviewed. There are various relevant studies that will be considered for the assessment of the legal aspects, e.g., Widrig 2015, Widrig/Tag 2014, Schöni 2014 and Kieser 2007.[81–84]

6.3.2 Study selection

A single researcher will screen and review the literature and identify studies relevant to the ELSO aspects. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, reports, legal documents, narrative research and case studies will be considered for inclusion. The publication language must be English, French, German, or Italian.

6.3.3 Data extraction, analysis and synthesis

The main ELSO aspects identified through this targeted search will be reported in a descriptive manner. Key issues will be summarised narratively, analysed, and discussed. For the analysis of ethical issues, an axiological approach through the “Hofmann catalogue” will be used, comprising 33 questions designed to identify characteristics of a health technology, involved interests and stakeholders. All relevant questions of the catalogue will be addressed.[85]

7. Summary and Outlook

Summary

In Switzerland, medicines containing valerian (alone or in combination) are widely used, and reimbursed for the treatment of symptoms related to insomnia, mental stress and test anxiety. To inform future reimbursement decisions, an HTA has been initiated to evaluate the clinical efficacy, effectiveness, safety, and ELSO aspects of these valerian-containing medicines compared to relevant alternatives for the above-mentioned indications. A budget impact analysis of valerian-containing medicines reimbursed in Switzerland will be conducted for the currently reimbursed populations. To provide an overview of the available evidence of cost-effectiveness from published literature, findings from the systematic literature review of economic evaluations will be extracted and summarised in narrative form.

The methodology consists of two systematic literature reviews; one focusing on RCTs, non-randomised controlled trials, and controlled observational studies and the other on health economic studies, as well as a targeted search addressing the ELSO domains. The search strategy will be conducted in multiple databases, and studies will be selected based on predefined inclusion and exclusion criteria. The quality of the included studies will be critically appraised, and the certainty of evidence of the extracted efficacy, effectiveness and safety data will be analysed using the GRADE approach. Where possible, the clinical information will be extracted and analysed using pairwise meta-analyses to estimate pooled effect estimates. In order to explore possible heterogeneity among pooled effect estimates and identify effect modifiers, subgroup analyses, as well as meta-regressions will be performed. Outcomes which cannot be summarised with pooled estimates will be analysed narratively by using the SWiM guideline. Findings from uncontrolled observational studies, identified through published systematic literature reviews and monographs, will be summarised and incorporated into the discussion and the assessment of the ELSO aspects. The review

of health economic evidence will summarise the results on costs and effects (both total per treatment group and incremental), the ICER, and budget impact of medicines containing valerian (alone or in combination). The budget impact analysis will show the budgetary impact from removing the above-mentioned products from the list of reimbursed medicines under the mandatory health insurance scheme. Data from Swiss health care claims, clinical guidelines, national formularies, and expert opinion will inform inputs for the model. Sensitivity analyses will explore uncertainties. ELSO aspects will be identified through screening and a literature review. Key ethical issues will be identified, analysed and discussed, using the Hoffmann catalogue. Results from the search and the presentation of ethical, legal, social, and organisational aspects of medicines containing valerian (alone or in combination) to treat symptoms of insomnia, mental stress and test anxiety will be displayed narratively.

It may be challenging to synthesize data if little evidence is available for specific subpopulations such as defined in PICO 3 and 4 (mental stress and test anxiety, respectively). Therefore, initially, the search will include studies with patients suffering from anxiety in general. Within this broader population, subgroup analyses can be conducted at a later stage, if permitted. Another key challenge concerns the inclusion of non-randomised trials and observational studies, which may be subject to a higher risk of bias due to their study design. Another significant challenge arises from the high heterogeneity across studies, particularly in terms of patient populations, assessed outcomes, and variations in valerian products. The latter includes differences in valerian extraction methods and formulations, which can influence the efficacy, effectiveness and safety outcomes. Additionally, a possible placebo effect may pose a challenge in evaluating the true efficacy and budget impact of valerian. Assessing the budget impact of valerian is further complicated by the potential therapy switches, as patients might transition between different treatments over time. Limited data on the diagnosis of individuals using these medicines presents another challenge for the budget impact analysis. Possible ethical challenges related to the use of valerian include considerations of patient autonomy and integrity, and social values around availability and performance in daily life.

Outlook

The HTA protocol is followed by the production of an HTA report. The objective of the HTA report is to generate a focused assessment of various aspects of medicines containing valerian for the treatment of symptoms related to insomnia, mental stress and test anxiety. 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 evidence

MEDLINE (Ovid)

Population	No search string
Intervention	Valerian/ or (valerian* or valeren* or baldrian* or "V. officinalis" or "V. radix").ti,ab,kw. or (Dormiplant or Hova or Redormin or Relaxane or Sedonium).ti,ab,kw. or ("Li 156" or "Ze 91019" or "Ze 185" or "WS 1014").ti,ab,kw.
Comparator	No search string
Outcomes	No search string
Limits	*Limit to humans* not (animals not humans).sh.
	Exclude infants not (exp infant/ not (exp child/ OR exp adolescent/ OR exp adult/))
	Exclude conference/congress abstracts limit X to (congress) → Then X not Y
	Limit to clinical studies[a] (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial or (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol) or Multicenter Study).pt. or Clinical Studies as Topic/ or exp Clinical Trials as Topic/ or Clinical Trial Protocols as Topic/ or Multicenter Studies as Topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or Placebos/ or Control Groups/ or Cross-Over Studies/ or (random* or sham or placebo*).ti,ab,hw,kf. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. or (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. or (phase adj6 (study or studies or trial*)).ti,ab,hw,kf. or ((crossover or cross-over) adj3 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial* or comparison*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.

Notes

[a]The clinical studies limit for MEDLINE via Ovid was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.[86]

Modifications include addition of the term "comparison*" to the proximity searches with crossover, open label, and equivalence/superiority terms, and removal of the animal study exclusion search terms. The "limit to humans" filter is applied to the search results in a subsequent step.

Embase (Elsevier)

Population	No search string
Intervention	'valerian'/exp OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix"):ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium):ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	*Limit to humans* NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))
	Exclude infants NOT ([infant]/lim NOT ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim))
	Exclude conference/congress abstracts NOT ([conference abstract]/lim)
	Limit to clinical studies[a] 'clinical study'/exp OR 'clinical trial (topic)'/exp OR 'clinical trial protocol'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR (random* or sham or placebo*):ti,ab,kw OR ((singl* or doubl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR ((tripl* or trebl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR (control* NEAR/3 (study or studies or trial* or group*)):ti,ab,kw OR (Nonrandom* or "non random*" or non-random* or quasi-random* or quasirandom*):ti,ab,kw OR (phase NEAR/6 (study or studies or trial*)):ti,ab,kw OR ((crossover or cross-over) NEAR/3 (study or studies or trial* or comparison*)):ti,ab,kw OR ((multicent* or "multi-cent*") NEAR/3 (study or studies or trial*)):ti,ab,kw OR allocated:ti,ab OR (("open label" or "open-label") NEAR/5 (study or studies or trial* or comparison*)):ti,ab,kw OR ((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial* or comparison*)):ti,ab,kw OR (pragmatic study or pragmatic studies):ti,ab,kw OR ((pragmatic or practical) NEAR/3 trial*):ti,ab,kw OR ((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)):ti,ab,kw OR trial:ti,kw

Notes

[a]The clinical studies limit for Embase via Elsevier was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.[86]

Modifications include removal of redundant subject headings; addition of the term "comparison*" to the proximity searches with crossover, open label, and equivalence/superiority terms; and removal of the animal study exclusion search terms. The "limit to humans" filter is applied to the search results in a subsequent step.

CENTRAL, Cochrane Protocols, Reviews and Trials (Cochrane Library via Wiley)

Population	No search string
Intervention	(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix"):ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium):ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as database is restricted to clinical studies in humans

APA PsycInfo (EBSCOhost)

Population	No search string
Intervention	TI(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR AB(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR TI(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR AB(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR TI("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014") OR AB("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	*Limit to humans* NOT ((DE "Animal Models" OR DE "Animals" OR DE "Animal Research" OR TI (animal model*)) NOT (DE "Human Males" OR DE "Human Females"))
	Limit to clinical studies[a] DE "Placebo" OR DE "Randomized Clinical Trials" OR DE "Randomized Controlled Trials" OR DE "Experiment Controls" OR DE "Clinical Trials" OR MR "CLINICAL TRIAL" OR TI ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR AB ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR SU ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR KW ("random*" OR "sham" OR "placebo*" OR "Nonrandom*" OR "non random*" OR "non-random*" OR "quasi-random*" OR "quasirandom*" OR "pragmatic study" OR "pragmatic studies") OR TI ((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR AB ((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR SU ((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR KW ((("singl*" OR "doubl*" OR "tripl*" OR "trebl*") W0 ("blind*" OR "dumm*" OR "mask*"))) OR TI ((("clinical" OR "crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR comparison*))) OR AB ((("clinical" OR "crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR comparison*))) OR SU ((("clinical" OR "crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR comparison*))) OR KW ((("clinical" OR

	"crossover" OR "cross-over" OR "multicent*" OR "multi-cent*" OR "equivalence" OR "superiority" OR "non-inferiority" OR "noninferiority" OR "quasiexperimental" OR "quasi-experimental") N2 ("study" OR "studies" OR "trial*" OR comparison*))) OR TI ((("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR comparison*))) OR AB ((("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR comparison*))) OR SU ((("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR comparison*))) OR KW ((("open label" OR "open-label") N4 ("study" OR "studies" OR "trial*" OR comparison*))) OR TI (("pragmatic" OR "practical") N2 ("trial*")) OR AB (("pragmatic" OR "practical") N2 ("trial*")) OR SU (("pragmatic" OR "practical") N2 ("trial*")) OR KW (("pragmatic" OR "practical") N2 ("trial*")) OR TI ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*")) OR AB ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*")) OR SU ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*")) OR KW ("control*" N2 ("study" OR "studies" OR "trial*" OR "group*")) OR TI (("phase") N5 ("study" OR "studies" OR "trial*")) OR AB (("phase") N5 ("study" OR "studies" OR "trial*")) OR SU (("phase") N5 ("study" OR "studies" OR "trial*")) OR KW (("phase") N5 ("study" OR "studies" OR "trial*")) OR TI "allocated" OR AB "allocated" OR SU "allocated" OR TI ("trial") OR KW ("trial")

Notes

[a]The clinical studies limit for APA PsycINFO via EBSCOhost was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.[86]
Modifications include addition of the term “comparison*” to the proximity searches with crossover, open label, and equivalence/superiority terms.

Web of Science Core Collection

Population	No search string
Intervention	TS=(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix") OR TS=(Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium) OR TS=("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	*Limit to clinical studies[a], Exclude animal studies, Exclude meeting abstracts* (TS=(random* or sham or placebo*) OR TS=((singl* or doubl*) NEAR/1 (blind* or dumm* or mask*)) OR TS=((tripl* or trebl*) NEAR/1 (blind* or dumm* or mask*)) OR TS=(control* NEAR/3 (study or studies or trial* or group*)) OR TS=(Nonrandom* or "non random*" or non-random* or quasi-random* or quasirandom*) OR TS=(phase NEAR/6 (study or studies or trial*)) OR TS=((cross-over or cross-over) NEAR/3 (study or studies or trial* or comparison*)) OR TS=((multicent* or "multi-cent*") NEAR/3 (study or studies or trial*)) OR TI=(allocated) OR AB=(allocated) OR TS=(("open label" or "open-label") NEAR/5 (study or studies or trial* or comparison*)) OR TS=((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial* or comparison*)) OR TS=(pragmatic study or pragmatic studies) OR TS=((pragmatic or practical) NEAR/3 trial*) OR TS=((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)) OR TI=(trial) OR AK=(trial)) NOT TI=(animal* OR mouse OR mice OR rat OR rats OR pig OR pigs) AND (Meeting Abstract (Exclude – Document Types))

Notes

[a]The clinical studies limit for Web of Science Core Collection was adapted by A. Berger (Liaison Librarian Medicine, University Library, University of Zurich) based on the Canadian Drug Agency Medline search filter.[86]

The filter was translated from Embase to Web of Science syntax and subject headings were removed. Modifications included addition of the term “comparison*” to the proximity searches with crossover, open label, and equivalence/superiority terms. The animal study exclusion search terms were removed. A title exclusion for animal terms will be applied to the search results in a subsequent step.

Clinicaltrials.gov

Population	No search string
Intervention	valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as registry consists of clinical studies in humans.

WHO International Clinical Trials Registry Platform Search Portal

Population	No search string
Intervention	*Simple search, including synonyms, all trial phases* valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"

Comparator	No search string
Outcomes	No search string
Limits	No limits applied as registry consists of clinical studies in humans. Limit for interventional studies is not available.

9.2 Search strategy for economic evidence

MEDLINE (Ovid)

Population	No search string
Intervention	Valerian/ OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix").ti,ab,kw. OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium).ti,ab,kw. OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014").ti,ab,kw.

Comparator	No search string
Outcomes	exp "Costs and Cost Analysis"/ OR Economics, Pharmaceutical/ OR exp Budgets/ OR models, economic/ OR (Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*).ti,ab,kw.
Limits	*Limit to humans* not (animals not humans).sh.
	Exclude infants not (exp infant/ not (exp child/ OR exp adolescent/ OR exp adult/))
	Exclude conference/congress abstracts limit X to (congress) → Then X not Y

Embase (Elsevier)

Population	No search string
Intervention	'valerian'/exp OR (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix"):ti,ab,kw OR (Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium):ti,ab,kw OR ("Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014"):ti,ab,kw

Comparator	No search string
Outcomes	'economic evaluation'/exp OR 'health care cost'/exp OR 'cost'/de OR 'budget'/de OR 'budget impact'/exp OR 'budget impact analysis'/exp OR 'budget impact model'/exp OR (Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*):ti,ab,kw

Limits	*Limit to humans* NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))
	Exclude infants NOT ([infant]/lim NOT ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim))
	Exclude conference/congress abstracts NOT ([conference abstract]/lim)

EconLit (EBSCOhost)

Population	No search string
Intervention	TI(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014") OR AB(valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	TI(Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*) OR AB(Cost* OR expenditure* OR financial* OR economic* OR price OR prices OR pricing OR "benefit-cost*" OR budget*)
Limits	No limits applied as search returned 1 result as of 1 April 2025

International Network of Agencies for Health Technology Assessment (INAHTA) database

Population	**No search string**
Intervention	"Valerian"[mh] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[Title] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[abs] OR (valerian* OR valeren* OR baldrian* OR (V. officinalis) OR (V. radix) OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR (Li 156) OR (Ze 91019) OR (Ze 185) OR (WS 1014))[Keywords]
Comparator	No search string
Outcomes	No search string
Limits	No limits applied

National Health Service Economic Evaluation Database (NHS EED)

Population	No search string
Intervention	*Simple search in "any field"* (valerian* OR valeren* OR baldrian* OR "V. officinalis" OR "V. radix" OR Dormiplant OR Hova OR Redormin OR Relaxane OR Sedonium OR "Li 156" OR "Ze 91019" OR "Ze 185" OR "WS 1014")
Comparator	No search string
Outcomes	No search string
Limits	No limits applied