Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

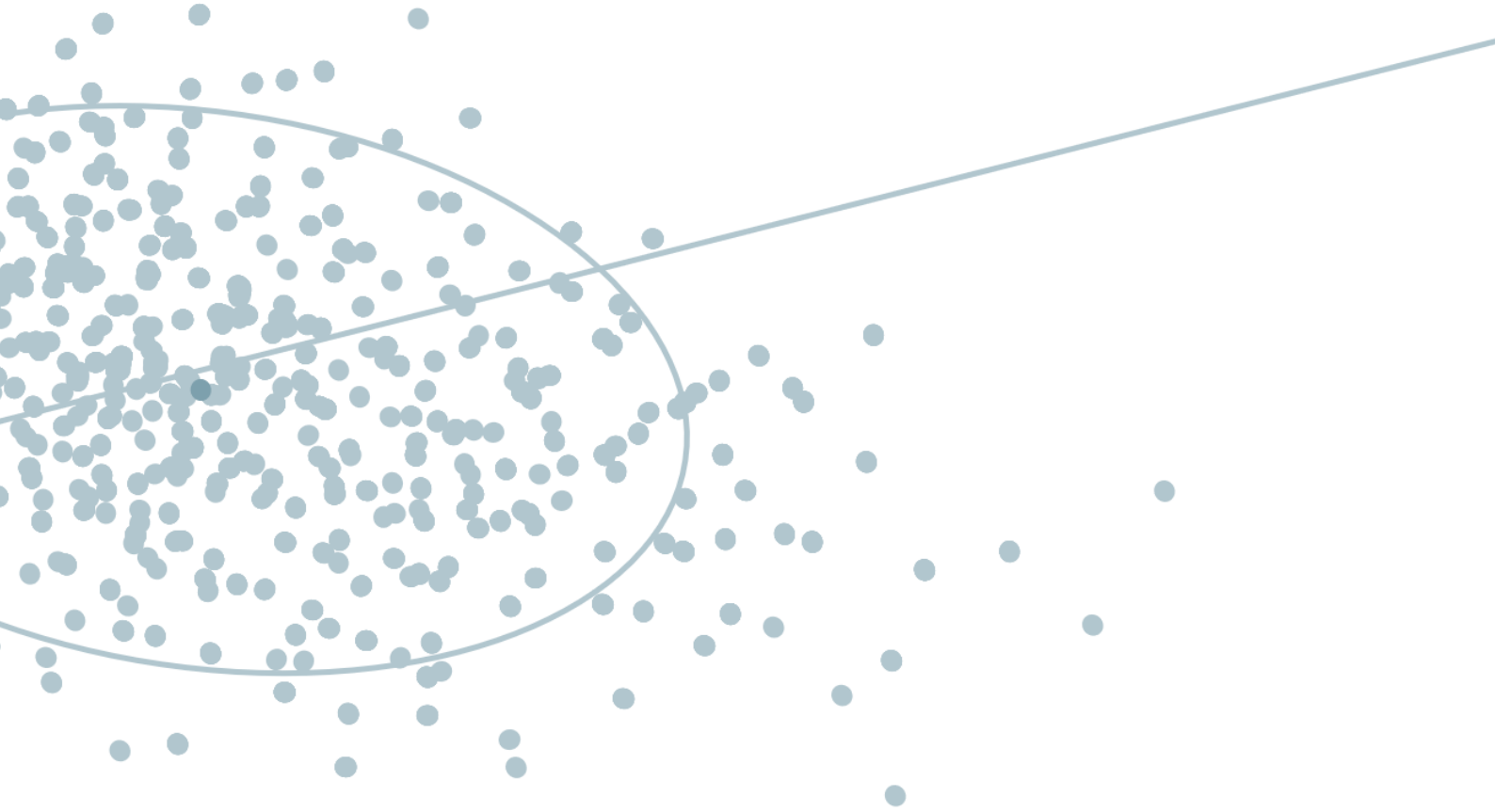
Federal Department of Home Affairs FDHA
Federal Office of Public Health FOPH

Health Technology Assessment (HTA)

HTA Protocol

Magnesium Supplementation

Version 17 April 2025



Title	Magnesium Supplementation
Technology	Magnesium (magnesium salts e.g. m. citrate, m. aspartate, m. oxide, combination of different salts)
Date	17 April 2025

Conflict of Interest:

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

Federal Office of Public Health FOPH
Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Switzerland
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

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

Executive Summary

The proposed health technology assessment (HTA) will evaluate oral magnesium supplements of ATC (Anatomical Therapeutic Chemical) category A12CC listed on the Swiss Spezialitätenliste that are currently reimbursed for a broad range of indications in Switzerland without limitation. To understand the current role and relevance of oral magnesium for the licensed indications in Swiss clinical practice, Swiss clinical experts and relevant clinical practice guidelines (CPGs) were consulted as part of the protocol development and both sources formed the basis for the refinement of the PICO criteria. Consequently, the proposed HTA will separately evaluate the safety, efficacy/effectiveness and budget impact of oral magnesium compared to placebo, no treatment, or standard of care in patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia, and in patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia. Ethical, legal, social and organisational issues associated with oral magnesium will also be investigated.

A systematic literature search of 4 databases (MEDLINE [Ovid], Embase [Ovid], Cochrane Library, INAHTA database) will be conducted. Randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs) that address the research questions will be considered. Included studies will be evaluated for risk of bias using study design-specific tools. The overall quality of the evidence will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. For each population, if ≥2 comparative studies (with the same comparator and study design) report an outcome of interest, a pairwise random-effects meta-analysis will be performed using an inverse-variance model. Where outcomes cannot be meta-analysed, results will be tabulated and described narratively. Searches will also be conducted in ClinicalTrials.gov and the EU Clinical Trials Register to identify ongoing clinical trials related to magnesium supplementation within the eligible populations.

A budget impact analysis will be conducted. The analysis will project costs in Swiss francs (CHF) to the payer over the next 5 years using selected current and possible future policy and pricing scenarios.

Ethical, legal, social and organisational issues will be addressed through systematic and targeted literature searches. The findings will be summarised narratively.

Table of Contents

Abbreviations and acronyms

AE	adverse event
ATC	Anatomical Therapeutic Chemical
CHF	Swiss franc
CI	confidence interval
CPG	clinical practice guideline
CT	computed tomography
EAE	effectiveness, appropriateness and economic efficiency
EQ-5D	EuroQol 5-dimension questionnaire
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public Health
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HRQoL	health-related quality of life
HTA	health technology assessment
ICD-11	International Classification of Diseases 11th Revision
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	intention to treat
IV	intravenous
MCID	minimum clinically important difference
MD	mean difference
NA	not applicable
NICE	National Institute for Health and Care Excellence
NRSI	non-randomised study of interventions
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio

PICO	population, intervention, comparator, outcome
PP	per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	randomised controlled trial
ROB 2.0	Cochrane Risk of Bias 2.0
ROBINS-I	Cochrane Risk of Bias in Non-randomised Studies of Interventions
RR	risk ratio
SD	standard deviation
SMD	standardised mean difference
WHO	World Health Organization

Objective of the HTA Protocol

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

1 Policy question and context

The HTA topic entails a policy question that will be informed by addressing HTA research questions (***Chapter 5***). In healthcare, a policy question is a request to regulate a reimbursement policy. It is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses uncertainty around a technology. This HTA report will address the following policy question: Should oral magnesium supplements (magnesium salts) continue to be reimbursed for patients without proven hypomagnesaemia, and if so for which indications?

Oral magnesium supplements are currently reimbursed for a broad range of indications in Switzerland without limitation; however, the clinical effectiveness of these magnesium salts in patients without proven hypomagnesaemia has been questioned.[1-4] Potentially relevant, licensed indications for oral magnesium that are of interest for this HTA are cardiovascular tachyarrhythmia, coronary heart disease, (pre-) eclampsia, tocolysis, tetanic syndrome, neuromuscular hyperexcitability, muscle cramps and prevention of recurrent calcium oxalate urolithiasis (a full list of licensed indications is reported in ***Appendix 11.2***). While magnesium is licensed for a variety of conditions, the scope of the proposed HTA has been refined via clinical expert consultation (and with consideration to relevant clinical practice guidelines [CPGs]) to focus on the most relevant conditions of calcium oxalate urolithiasis[1] and muscle cramps.[2-4] (For a more detailed explanation of the refinement process refer to ***Chapter 2.1***). To inform the policy question, the HTA report will evaluate the evidence pertaining to the effectiveness, appropriateness and economic efficiency (EAE) (specifically relating to budget impact) of oral magnesium for muscle cramps and calcium oxalate urolithiasis. Cost-effectiveness outcomes are specifically out of scope for this proposed HTA.

2 Medical background

2.1 Medical context of eligible indications

Magnesium is an essential electrolyte. Its primary function is to act as a co-factor in enzyme systems that regulate biochemical reactions, including protein synthesis, muscle and nerve function, blood glucose control and blood pressure regulation.[5] It is required for energy production, oxidative phosphorylation and glycolysis.[6] Magnesium also plays a role in the active transport of calcium and potassium ions across cell membranes, which is important to enable nerve impulse conduction, muscle contraction and cardiac rhythm.[7] Thus, magnesium may be involved in many disease processes.

Magnesium is licensed for a variety of conditions in Switzerland, including but not limited to hypomagnesaemia, insufficient intake due to a low-magnesium diet, restless leg syndrome, (pre-) eclampsia, muscle cramps and calcium oxalate urolithiasis (see ***Appendix 11.2*** for a list of indications for magnesium supplements licensed in Switzerland). To make the scope feasible for an HTA, the list of licensed Swissmedic indications was refined during development of the protocol. Indications for which it is clear that patients should be prescribed magnesium have been excluded (e.g. known hypomagnesaemia, or conditions or prescribed medications that predispose patients to hypomagnesaemia).[8] Primary prevention with oral magnesium (aiming to prevent a disorder before it occurs) does not fall within the remit of this HTA, therefore primary prevention of muscle cramps or calcium oxalate urolithiasis will not be investigated in this HTA. Relevance for the Swiss context of the remaining licensed indications was determined in the planning phase of the protocol through consultation with Swiss clinical experts and with consideration to relevant CPGs (see ***Appendix 11.3*** and ***Appendix 11.4*** for an overview of the recommended use of oral magnesium in the licensed indications per CPGs and Swiss clinical expert consultation).[1,2] As a result, the indications included as the focus of this HTA are muscle cramps and calcium oxalate urolithiasis (kidney stones). The remaining indications have been excluded (see ***Appendix 11.4*** for reasons for exclusion).

2.2 Calcium oxalate urolithiasis

Calcium oxalate urolithiasis, colloquially known as calcium oxalate kidney stones, are solid crystalline masses that form throughout the urinary tract.[9] Calcium oxalate urolithiasis formation is a complicated process with various contributing factors, the most significant being urinary solute supersaturation.[9] Supersaturation is a state where the solute in a solution is greater than its solubility, leading to accumulation of solutes, which then form solid crystalline masses.[9] While supersaturation is necessary, it is not the sole cause of calcium oxalate urolithiasis development. Various factors can contribute to supersaturation, such as urine volume, urine pH, diet, genetics, and the presence or absence of minerals such as citrate, pyrophosphate and magnesium, which can act as inhibitors for crystal formation and also contribute to the development of calcium oxalate

urolithiasis.[9] Urine pH, for example, can modify the solubility of the solutes, which can impact the formation of calcium oxalate urolithiasis.[9]

While Switzerland-specific incidence and prevalence rates for urolithiasis are unknown, approximately 15% of the global population will develop calcium oxalate urolithiasis during their lifetime.[10,11] The most common form of urolithiasis is masses composed of calcium oxalate, accounting for approximately 64% of all urolithiases.[12] Lifetime recurrence of urolithiasis is approximately 50%.[13]

Symptoms and costs associated with calcium oxalate stones can be significant. Primary symptoms of urolithiasis include pain in the kidney, renal colic, and blood in the urine. Renal colic can be complicated by kidney infection, sepsis, and fornix rupture.[9] Treatment of urolithiasis and its associated symptoms imposes a large economic burden globally, with expenses increasing over time.[14] While Swiss-specific data are unavailable, in the United States (US) the annual estimated financial burden (direct and indirect costs) was US$5.3 billion in 2005.[15] In the United Kingdom (UK), it was estimated that total initial (1-year) costs were between £950,842 and £2,336,442 in 2010.[16]

Regarding acute clinical management of renal colic, smaller urolithiases can often be diagnosed and conservatively managed by a general practitioner (GP), whereas patients with larger symptomatic stones or signs of infection should be referred to the emergency department and may need to be managed as an inpatient.[9] In cases where the stones are smaller, it may be possible to pass them naturally without medical intervention; however, in more severe cases, clinical interventions may be needed to remove the urolithiasis, including double J catheter insertion, shock wave lithotripsy, cystoscopy, ureteroscopy or percutaneous nephrolithotomy.[1,17]

Secondary prevention of recurrent stones differs based on the stone composition but generally involves dietary and lifestyle changes including increasing fluid intake and diet modification, and pharmacological interventions including thiazide diuretics and citrate salts.[1,17] Various laboratory and imaging tests may be performed to diagnose the presence and type of urolithiasis, the most common being blood tests, stone composition analysis and 24-hour urinalysis to check mineral levels in the blood and urine, in addition to computed tomography (CT) scans and/or ultrasound.[1,18-20]

2.3 Muscle cramps

Muscle cramps are sudden, involuntary painful contractions of a muscle, which are self-extinguishing within seconds to minutes and often accompanied by a palpable knotting of the muscle.[21] The terms *cramp* and *spasm* are often used interchangeably; however, they represent different underlying pathophysiological processes.[21] Muscle spasm is a broader term, referring to any involuntary and abnormal muscle contraction, regardless of whether it is painful.[21-23] Muscle spasms typically involve prolonged co-contractions of more than one muscles, producing slow, twisting, and repetitive movements or abnormal postures that are not relieved by muscle

stretching.[21] In contrast, cramps have a distinct clinical presentation, characterised by: (a) intense pain that may cause lingering soreness or elevated levels of muscle proteins in the blood; (b) a sudden, involuntary onset with gradual spontaneous resolution or abrupt relief through stretching; (c) involvement of only a single muscle or part of a muscle; (d) both mild and forceful contractions, often occurring when the muscle is shortened; and (e) a tendency to affect the calves and feet most frequently, followed by the hamstrings and quadriceps.[21]

Self-limiting muscle cramps are common, with the incidence per year estimated at 36% in otherwise healthy adults, as reported in an epidemiological survey conducted in the Netherlands in 1988.[24] Pregnant women frequently experience muscle cramps, particularly leg cramps during the third trimester, with data showing that the prevalence of leg cramps in pregnant women was 55% in a prospective clinical trial conducted in Iran in 2009.[25] Additionally, populations including the elderly and athletes have been found to have an increased likelihood of muscle cramps.[26,27] Adults older than 60 years of age in primary care, reported the prevalence of nocturnal leg cramps to be 46% in a cross-sectional study conducted in France in 2011–2012.[28]

The specific aetiology of muscle cramps unassociated with an underlying medical condition is unknown and context-dependent.[29] Conditions associated with muscle cramps include, but are not limited to, neuromuscular disorders, metabolic disorders such as hypothyroidism, adrenal insufficiency, hypoparathyroidism, electrolyte imbalances, malnutrition, alcoholism and liver cirrhosis.[2] There are many types of cramps, including, but not limited to, idiopathic cramps of unknown cause (e.g. nocturnal leg cramps), pregnancy-associated cramps and exercise-associated muscle cramps.[29]

Muscle cramps are most commonly diagnosed in the primary care setting via a clinical history based on symptoms and blood tests (***Table 1***).[2,30] Treatment depends on whether an underlying condition is present, in which case the focus should be on treating the underlying cause.[2]

While treatment options may be specific to the type of cramps or underlying condition, some general treatment strategies may be recommended, comprising pharmacological and non-pharmacological interventions. Non-pharmacological interventions include stretching, massage, cryotherapy/thermotherapy, hydration and ensuring electrolyte levels are balanced.[2] Pharmacological treatments include magnesium supplements, benzodiazepines and pain relievers such as non-steroidal anti-inflammatory drugs (NSAIDs).[2,31]

Table 1 Basic laboratory blood tests for diagnosis and management of muscle cramps

Basic diagnostic tests
Blood count, electrolytes (Na, K, Mg, Ca), blood sugar, creatinine, GFR, urea, CK, GOT, TSH

Abbreviations: **Na** = sodium; **K** = potassium; **Mg** = magnesium; **Ca** = calcium; **GFR** = glomerular filtration rate; **CK** = creatine kinase; **GOT** = glutamic-oxaloacetic transaminase; **TSH** = thyroid-stimulating hormone.

3 Technology

3.1 Technology description

Magnesium supplements come in various compounds, including magnesium aspartate, magnesium oxide, magnesium sulphate and magnesium citrate. The key difference between compounds relates to the level of bioavailability, or how easily the magnesium can be absorbed, and their tolerability. Magnesium aspartate and magnesium citrate are generally well-tolerated, have similar levels of bioavailability and are absorbed more easily than magnesium oxide; however, they have lower amounts of elemental magnesium.[32] In comparison, magnesium oxide and magnesium sulphate have poor tolerability at high doses, and have lower bioavailability but higher levels of elemental magnesium.[32,33]

The proposed HTA will evaluate oral magnesium preparations of ATC (Anatomical Therapeutic Chemical) category A12CC listed on the Swiss Spezialitätenliste. Nine oral magnesium supplements are currently reimbursed in Switzerland:

- Magnesiocard® (Biomed AG) – magnesium aspartate
- Magnesium Sandoz® (Sandoz Pharma AG) – magnesium aspartate and citrate
- Mg5-Granoral® (OM Pharma Suisse SA) – magnesium aspartate
- Mg5-Longoral® (OM Pharma Suisse SA) – magnesium aspartate
- Mg5-Oraleff® (OM Pharma Suisse SA) – magnesium aspartate
- Magnesium-Diasporal® Citracaps (Doetsch Grether AG) – magnesium citrate
- Magnesium-Diasporal® Granulat (Doetsch Grether AG) – magnesium citrate
- AndreaMag® (Andreabal AG) – magnesium oxide
- Solmag 300® (Nutrimed AG) – magnesium oxide

3.2 Mechanism of action

3.2.1 Calcium oxalate urolithiasis

Magnesium is understood to inhibit the formation of calcium oxalate stones primarily by competing with calcium for oxalate binding—reducing the concentration of oxalate available for calcium stone formation, and reducing the interaction of calcium ion and oxalate ion pair interactions.[34-36] Additionally, the citrate component in magnesium citrate compounds can alkalinise urinary pH, making the environment less favourable for crystal formation and resulting in a decreased likelihood of calcium oxalate stone formation.[37] Citrate salts (regardless of formulation) compete with oxalate for the availability of urinary calcium for bonding with oxalate (insoluble) and eliminating calcium in a citrate salt, which is highly soluble.[38] Despite evidence from in vitro, animal and simulation studies demonstrating the inhibitory action of magnesium on calcium oxalate stone formation, the clinical

role of magnesium compounds is a matter of ongoing debate owing to conflicting results from clinical trials.[36]

3.2.2 Muscle cramps

The exact mechanism of action of magnesium on reducing the severity and frequency of muscle cramps is unclear and likely specific to the underlying medical condition (if one exists). One proposed mechanism of action is that the threshold of axon stimulation is decreased and nerve conduction velocity increased in cases where magnesium levels are depleted, leading to increased excitability of nerves and muscles.[4] Magnesium depletion may result in neuronal excitability and increased neuromuscular transmission.[4] Magnesium supplementation may promote glucose uptake and prevent the accumulation of lactate in skeletal muscle, thus potentially leading to a reduction in pain after contraction of a muscle.[4]

4 Population, intervention, comparator, outcome

The PICO criteria are defined as follows:

Calcium oxalate urolithiasis

P:	Patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia
I:	Oral magnesium supplements (as listed on Spezialitätenliste)* – magnesium citrate – magnesium oxide
C:	Placebo, no treatment, or standard of care (e.g. clear fluid intake, diet modification, potassium citrate salts, thiazide)
O:	Patient relevant outcomes: – stone recurrence (symptomatic or radiological) – stone size – AEs (e.g. gastrointestinal) – compliance/adherence – HRQoL Economic outcomes: – cost, budget impact

Abbreviations: AEs = adverse events; **HRQoL**= health-related quality of life.
Note: * All magnesium supplements listed on the Spezialitätenliste are classed as magnesium salts.

Muscle cramps

P:	Patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia
I:	Oral magnesium supplements (as listed on Spezialitätenliste)* – magnesium aspartate – magnesium citrate – magnesium oxide
C:	Placebo, no treatment, or standard of care (e.g. stretching, benzodiazepines, use of pain relievers, hydration, massage, or cryotherapy/thermotherapy)
O:	Patient relevant outcomes: – muscle cramp frequency – muscle cramp severity – muscle cramp duration – AEs – compliance/adherence – HRQoL Economic outcomes: – cost, budget impact

Abbreviations: AEs = adverse events; **HRQoL** = health-related quality of life.
Note: * All magnesium supplements listed on the Spezialitätenliste are classed as magnesium salts

4.1 Population

4.1.1 Calcium oxalate urolithiasis

The first population of interest to this HTA (population 1) includes patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia. It is important to note that in Switzerland, magnesium is only licensed to be prescribed to prevent the recurrence of urolithiasis (i.e. secondary prevention). Therefore, the use of magnesium to treat urolithiasis during an event is not licensed, along with the treatment of patients with residual calcium oxalate stones.

Notably, the definitions of hypomagnesemia that are used to exclude patients in the primary evidence will be taken into consideration during the HTA phase. Meaning, if a study says it has excluded patients with hypomagnesemia, this will be taken at face value. Where possible (if reported), the magnesium status of included patients will be documented and discussed. The external validity and transferability of these definitions to Switzerland will be assessed in the full HTA.

4.1.2 Muscle cramps

The second population of interest to this HTA (population 2) includes patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia. Cramps will be differentiated from spasms where possible, according to the definitions provided in ***Section 2.3***. Where study authors have not differentiated between cramps and spasms, inclusion will be based on the definition of cramp provided by the study authors.

As aforementioned, the definitions of hypomagnesemia that are used to exclude patients in the primary evidence will be taken into consideration during the HTA phase. Meaning, if a study says it has excluded patients with hypomagnesemia, this will be taken at face value. Where possible (if reported), the magnesium status of included patients will be documented and discussed. The external validity and transferability of these definitions to Switzerland will be assessed in the full HTA.

4.2 Intervention

The intervention of interest to this HTA is oral magnesium. Based on the licensed indications of the reimbursed oral magnesium supplements (***Table 10***), magnesium citrate and magnesium oxide will be considered relevant for calcium oxalate urolithiasis, whereas magnesium aspartate, magnesium citrate and magnesium oxide will be considered relevant for muscle cramps.

Oral magnesium supplements of any brand and duration of treatment will be considered relevant to this HTA, to ensure that the full range of available evidence is captured. Dose will be guided by the standard dose of the magnesium supplements listed on Swissmedic (***Table 10***).

Any differences in these magnesium supplements to those listed on the Swiss Spezialitätenliste will be discussed in the 'Applicability of evidence to the Swiss clinical practice' section of the full HTA.

As per the prescription and application information on Swissmedic, oral magnesium supplementation is not recommended for children under the age of 4 years. Therefore, as part of the eligibility criteria for this HTA, participants must be aged ≥4 years to be considered for inclusion.

4.3 Comparator

4.3.1 Calcium oxalate urolithiasis

First-line prevention of urolithiasis, regardless of composition, is dietary and lifestyle changes including increasing clear fluid (excluding sugar-sweetened beverages) intake to 2.5–3 L per day and consuming a balanced diet.[1] More specific recommendations for prevention of calcium oxalate stones include adequate calcium intake and limiting oxalate-rich foods (e.g. spinach, beets, nuts).[1,39] Second-line prevention methods other than magnesium supplementation may include the use of other citrate salts (i.e. potassium or sodium instead of, or in combination with, magnesium) that have an alkalinising effect.[1] Per clinical expert advice, potassium salts (e.g. Urocit®) are

generally preferable, as they have a greater alkalinising effect than magnesium or sodium citrate salts.[40] Thiazide diuretics (e.g. Esidrex®) are another commonly used option, which work by assisting with the reabsorption of calcium in the kidneys, thereby reducing urinary calcium excretion and decreasing the risk of calcium crystal formation.[41] Magnesium is also sometimes provided as an adjuvant therapy to thiazides, as the latter can reduce the amount of available magnesium meaning patients may require supplementation.[40,41] In addition to the above comparators, placebo and no treatment are also relevant comparators for this protocol. Advice from a local clinical expert suggests that citrate salts (particularly potassium citrate) is the most relevant comparator for Swiss clinical practice.[40]

4.3.2 Muscle cramps

In addition to magnesium, CPGs recommend static stretching as an alternative or adjuvant treatment of cramped muscles.[2] Quinine sulphate is a historical treatment that was moderately effective in reducing muscle cramps; however, it was taken off the market in Switzerland after an alert by the US Food and Drug Administration in 2006 due to risk of serious adverse events (AEs).[42] For this reason, it will not be considered as a relevant comparator in the proposed HTA. While other pharmacological and non-pharmacological treatments such as benzodiazepines (e.g. diazepam), use of pain relievers (e.g. paracetamol, NSAIDs), hydration, massage and, cryotherapy/thermotherapy have been suggested as potential treatment options, they are not well supported by evidence in the guidelines.[2,31] In addition to the above comparators, placebo and no treatment are also relevant comparators for this protocol. Along with the potential comparators identified via CPGs, advice from a local clinical expert suggests that static stretching is the most relevant comparator for Swiss clinical practice.[43]

4.4 Outcomes

4.4.1 Calcium oxalate urolithiasis

4.4.1.1 Stone recurrence rate

Due to magnesium's proposed mechanism of action, which aims to inhibit the formation of calcium oxalate stones, stone recurrence (i.e. formation of new stones) is the primary outcome of interest for this indication. The stone recurrence rate may be presented as the percentage of participants who develop a new stone over a defined time period, demonstrated via medical imaging (e.g. abdominal radiography, intravenous urography, CT), or the number of new stones per patient per defined time period.[44]

4.4.1.2 Stone size

Smaller uroliths are easier to pass and may not require medical intervention, whereas stones larger than 7 mm will likely be unable to pass without medical intervention.[45] In cases of stone recurrence, even if magnesium cannot prevent the development of a new stone, it may prevent the development of large stones or prevent pre-existing stones from getting larger. Therefore, stone

size is an outcome of interest, as assessed via medical imaging (e.g. abdominal radiography, intravenous urography, renal ultrasound, CT).[38] Along with stone size, reported medical interventions required to remove/break-down stones will also be described.

4.4.1.3 Adverse events

AEs are any negative events that occur during treatment, so AEs are important for assessing treatment safety.[46] They can be reported in various ways, most commonly as the proportion of patients who experience a particular AE, or as the number of patients reporting a particular AE.[46] This outcome is also relevant to muscle cramps (not duplicated in ***Section 4.4.2*** to avoid repetition).

4.4.1.4 Compliance/adherence

According to the World Health Organization (WHO), adherence is defined as 'the extent to which a person's behaviour—taking medication, following a diet and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider.'[47] Compliance/adherence to a treatment regimen of magnesium supplementation is an outcome of interest. It is also linked to AEs, because patients who experience AEs are less likely to adhere to the treatment plan.[47] This outcome is also relevant to muscle cramps (not duplicated in ***Section 4.4.2*** to avoid repetition).

4.4.1.5 Health-related quality of life

According to Patrick and Erikson, health-related quality of life (HRQoL) refers to 'the value assigned to the duration of life as modified by the impairments, functional status, perceptions and social opportunities that are influenced by disease, injury, treatment or policy.'[48] It is important to assess this outcome, as it is well known that the pain associated with urolithiasis can contribute to a reduction in HRQoL.[49,50] The Urinary Stones and Intervention Quality of Life (USIQoL) tool is a urolithiasis-specific HRQoL tool.[51] Other generic tools, such as the EuroQol 5-dimension questionnaire (EQ-5D)[52] and the Short-Form Health Survey (SF-12/36) will also be of interest.[53,54]

4.4.2 Muscle cramps

4.4.2.1 Muscle cramp frequency

One of the primary goals in treating muscle cramps is to reduce the frequency of cramp occurrence, therefore this is a key outcome of interest. Patient-reported cramp frequency can be measured as the percentage change from baseline over a given time period (e.g. 4 weeks), the mean number of cramps over a given time period, or the number of patients reporting cramp reduction of ≥25% over a given time period.[3]

4.4.2.2 Muscle cramp severity/intensity

Reduction in cramp severity/intensity is another primary goal of treatment. Cramp severity/intensity is usually patient-reported and can be measured using a pain scale (e.g. visual analogue scale, numerical rating scale) or by the number/proportion of patients reporting a particular pain severity (low–high) over a given time period.[3,55]

4.4.2.3 Muscle cramp duration

Cramp duration is another outcome of interest. Muscle cramp duration is typically patient-reported and may be measured as a continuous variable (e.g. duration in minutes) or a categorical variable (e.g. number of cramps persisting >1 minute).[3]

4.4.2.4 Health-related quality of life

It is important to assess this outcome as it is well known that muscle cramps can contribute to a reduction in HRQoL.[56,57] No validated cramp-specific HRQoL tools have been identified, therefore generic HRQoL tools (e.g. EQ-5D, SF-12/36) may be of interest.

5 HTA research questions

To evaluate the technology, the following research questions will be addressed, covering the central HTA domains as designated by the EUnetHTA core model (clinical effectiveness; safety; budget impact; and ethical, legal, social and organisational aspects).

1.1. Is oral magnesium supplementation effective/efficacious compared to placebo, no treatment or standard of care in patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia?

1.2. Is oral magnesium supplementation effective/efficacious compared to placebo, no treatment or standard of care in patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia?

2.1. Is oral magnesium supplementation safe compared to placebo, no treatment or standard of care in patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia?

2.2. Is oral magnesium supplementation safe compared to placebo, no treatment or standard of care in patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia?

3.1. What is the budget impact of oral magnesium supplementation in Switzerland for treatment of calcium oxalate urolithiasis and muscle cramps?

4.1. Are there ethical, legal, social or organisational issues related to oral magnesium supplementation for calcium oxalate urolithiasis and muscle cramps?

6 Methodology

The proposed methods have been developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5).[58] They are described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.[59]

6.1 Databases and search strategy

A systematic literature search will be conducted in 4 biomedical databases (Medline, Embase, Cochrane Library, INAHTA HTA database). The draft search strategy, including medical subject headings and keyword search terms related to the population and intervention, is presented in ***Appendix 11.1***. The search strategy includes filters to exclude non-human studies. Filters will be used to limit search results to studies published in English, and in French, German and Italian (3 of the 4 official languages of Switzerland. Romansh will not be included because of the limited number of publications available.) Search filters will also be used to exclude letters, editorials and conference proceedings. No date limits will be applied to the searches. In addition to database searches, reference lists from systematic reviews addressing the PICO criteria and from included primary studies will be screened for relevant articles (backwards citation searches). Studies that cite included primary studies will also be screened (forwards citation searches).

Searches will be conducted in ClinicalTrials.gov and the EU Clinical Trials Register to identify ongoing clinical trials related to magnesium supplementation in the eligible populations. In addition, INAHTA member HTA agency websites will be searched to identify HTA reports not indexed in the HTA database. ***Appendix 11.1*** outlines the planned search strategy for each database.

The draft search strategy was validated by comparing the search results against known literature addressing the research questions. A targeted scoping search for existing systematic and narrative reviews on the use of magnesium supplementation for calcium oxalate stones and muscle cramps was conducted. These searches yielded 3 relevant reviews related to calcium oxalate urolithiasis,[60-62] and 4 reviews related to muscle cramps.[3,63-65] Primary studies included in these reviews that met the inclusion criteria for the present HTA were checked against the draft search results. Search terms were revised until all relevant published articles appeared in the draft search results.

6.2 Study selection

Results from the literature searches will be imported into Rayyan (Rayyan Systems Inc, US).[66] Rayyan functions similarly to EndNote, but allows for easy blinding of reviewers and management of study inclusion conflicts. The search results will be screened against the predetermined eligibility criteria by 2 reviewers in duplicate (***Table 2***). Studies will first be screened by title and abstract, followed by full-text review of potentially relevant publications. Upon completion of each stage of screening, conflicts between reviewers on study inclusion will be settled via consensus. If consensus cannot be reached, a third reviewer will decide whether to include or exclude the

citation. Reasons for excluding articles at full-text review will be documented and the results of the study selection will be reported in a PRISMA flow diagram.

Studies will be prioritised for inclusion by study design using a hierarchical selection process. For each population, RCTs meeting the predetermined inclusion and exclusion criteria will be included to assess the clinical effectiveness and safety of magnesium supplementation. Comparative RCTs that include cross-over (with or without a washout period) will be eligible for inclusion, but only data for the first assigned treatment up until cross-over will be included, due to the likely continued therapeutic effect from magnesium that has been stored intracellularly and absorbed into bone.[67] If no RCTs are identified for a particular population, then prospective non-randomised studies (NRSIs) that are propensity score-matched—to ensure confounding factors are adjusted for—will be included (hereon referred to as NRSIs). NRSIs will only be considered for inclusion if they are comparative, with a defined control arm. Furthermore, if no data are identified from RCTs for the prespecified outcomes (outlined in ***Section 4.4***), a sequential approach will be taken to query whether these outcomes have been reported in the identified NRSI.[68]

Table 2 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population 1 (P1)	Patients aged ≥4 years with prior calcium oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia†	- Patients aged <4 years - Patients with proven hypomagnesaemia† - Treatment of existing (primary, residual etc.) stones - Patients without existing calcium oxalate lithiasis (i.e. primary prevention)
Population 2 (P2)	Patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia*†	- Patients aged <4 years - Patients with proven hypomagnesaemia† - Patients without existing cramps (i.e. primary prevention)
Intervention	Oral magnesium (any brand and treatment duration) Compound of interest (per Swissmedic): - P1: magnesium citrate, magnesium oxide - P2: magnesium aspartate, magnesium citrate, magnesium oxide	- Intravenous magnesium - Intramuscular magnesium - Transdermal magnesium
Comparator	Placebo, no treatment, standard of care (per PICO defined in ***Section 4***)	N/A
Outcomes	Patient relevant and economic outcomes, as defined in ***Section 4***	Inadequate data (incongruous data reported between figures and text etc.), incomplete reporting,, any other outcomes
Language	English, French, German, Italian	All other languages
Study design	Studies selected based on the following hierarchy of study design, with preference given for the highest level of evidence: 1. RCTs – comparative 2. NRSIs – prospective, comparative (with control arm), propensity score-matched (study design-specific details ***Section 6.2***)	Systematic reviews, single-arm studies, case reports, conference abstracts, letters to the editor, expert opinion, brief communications, editorials, narrative review articles, non-human/laboratory studies

Abbreviations: N/A = not applicable; **NRSI** = non-randomised study of interventions; **RCT** = randomised controlled trial

Notes: *Cramps will be differentiated from spasms where possible, according to the definitions provided in ***Section 2.3***. Where study authors have not differentiated between cramps and spasms, inclusion will be based on the definition of cramp provided by the study authors.

† The definitions of hypomagnesemia that are used to exclude patients in the primary evidence will be taken into consideration during the HTA phase. Meaning, if a study says it has excluded patients with hypomagnesemia, this will be taken at face value. The external validity and transferability of these definitions to Switzerland will be assessed in the full HTA.

6.3 Data extraction

One reviewer will independently extract data (at trial/study-arm level) into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or utilisation of a third independent reviewer. Data of interest include:

– study information: trial identifier, author, country, year, number of institutions, setting (hospital, community care etc.), study design, length of follow-up, inclusion/exclusion criteria (notably, the definition of hypomagnesemia used to exclude patients)

– demographic information: number of enrolled participants, number lost to follow-up, age, gender, ethnicity, comorbidities, population (e.g. muscle cramps or calcium oxalate urolithiasis), magnesium status

– intervention and comparator: type/brand of magnesium (i.e. compound/active ingredient), administration route (i.e. oral) and frequency, dosage, duration of treatment, type of comparator (including dosage and regimen), and concomitant and prior interventions (name, dosage, regimen)

– prespecified outcomes: number of events; change scores (ANCOVA-adjusted), mean change from baseline or baseline and final follow-up scores with standard deviation (SD) or other measures of variance (e.g. standard error [SE], 95% confidence intervals [CI]) for the outcomes of interest:

    - effectiveness outcomes – intention to treat (ITT) population (preferred) or per protocol (PP) population if ITT data unavailable. Analyses adjusted for baseline covariates will be preferentially extracted; where no adjustments have been conducted, unadjusted data will be extracted
    - safety outcomes – PP population data or ‘as treated’ population data

– other noteworthy features (e.g. effect modifiers), limitations.

For studies that report outcomes graphically instead of numerically, WebPlotDigitizer will be used to estimate numerical values.[69]

6.4 Quality appraisal

Assessment of the risk of bias in included studies will be performed in duplicate. Any differences will be settled via consensus. If consensus cannot be reached, a third reviewer will be consulted.

Risk of bias of included evidence will be assessed using different tools depending on the research design. Randomised controlled trials (RCTs) will be evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0).[70] Non-randomised studies of interventions (NRSIs) will be evaluated using the Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS–I V2) tool.[71] Risk of bias (RoB) will be conducted at the outcome level. For brevity, outcomes that receive the same overall RoB rating from the RoB assessment will be grouped for reporting purposes.

The overall quality of the evidence will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[72-74] The GRADEpro guideline development tool (GDT) will be used to construct the summary of evidence tables.[72] One reviewer will appraise the outcomes using GRADE, which will then be checked by a second reviewer. Any differences will be settled via consensus. If consensus cannot be reached, a third reviewer will be consulted.

A list of potential confounding factors relevant to the assessment of RoB in NRSIs via ROBINS-I V2 is outlined in ***Appendix 11.5***.

6.5 Data analysis of efficacy/effectiveness and safety outcomes

6.5.1 Data synthesis

De novo meta-analyses will be performed for outcomes of interest from primary research reports of RCTs or NRSIs, separately, based on study design. Data for each population of interest will be analysed separately. Similarly, data for each class of comparator will be analysed separately. Only direct comparative evidence will be considered. Network or indirect meta-analyses are outside the scope of this review.

Meta-analysis will be considered when at least 2 RCTs or NRSIs reporting the same outcome(s) with the same population, intervention and comparator group are identified (but separately based on study design). Pooling of data for meta-analysis will only be conducted where clinical and methodological characteristics are consistent (i.e. low heterogeneity).

Meta-analysis will be performed using R software.[75,76] Preferentially, random-effects models using the generic inverse variance method will be used as the basis for the primary analysis. Common-effects models using the generic inverse variance method will only be used in cases where it is reasonable to assume that the studies are measuring the same treatment effect (i.e. due to low clinical, statistical and methodological heterogeneity between included studies). Random-effects models will be used in all other cases.[77]

Each dichotomous outcome will be reported as a risk ratio (RR) or odds ratio (OR) with 95% CIs. Where possible, ORs will be converted to RRs to allow for ease of interpretation of dichotomous outcomes. The unit of measurement will be the number of patients experiencing an event. Continuous outcomes will be reported as mean difference (MD) between treatment arms, with 95% CIs. Where included studies report different outcome scales, standardised mean difference (SMD)

with 95% CI will be used. SMDs will be interpreted using generic SD units and also re-expressed as the most commonly reported scale included in the analysis.

MDs will be interpreted as clinically meaningful based on minimum clinically important differences (MCIDs) (not yet identified). Where an MCID is not defined for an outcome, only the point estimate, measure of variance and statistical significance will be reported, and caution will be recommended when interpreting the result. SMDs will be interpreted following recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5), whereby an SMD of 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect.[58] Where an SMD is re-expressed into the units of a specific measurement instrument, the result will be interpreted according to the MCID associated with that instrument.

All dichotomous outcomes will be reported at longest follow-up. Where dichotomous outcomes data are too heterogenous to pool at longest follow-up, data will be pooled at specific timepoints. Depending on data availability for continuous outcomes, data will be pooled at specific timepoints. Based on the initial literature scoping, specific follow-up timepoints for which data may be pooled are 4 weeks, 8 weeks and 12 weeks for both dichotomous and continuous outcomes.[1-3,78]

6.5.2 Assessment of statistical heterogeneity

Statistical heterogeneity will be assessed graphically via forest plots. Heterogeneity will be assessed statistically using the Chi^2 test ($p < 0.10$ representing significant heterogeneity) and the I^2 statistic for the meta-analysis of dichotomous outcomes, and Tau^2 and I^2 for continuous outcomes. The thresholds for low, moderate, substantial and considerable heterogeneity will be those proposed in the Cochrane Handbook for Systematic Reviews of Interventions (I^2 = 0–40%, might not be important; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; 75–100%, considerable heterogeneity).[58] Where substantial heterogeneity is evident, the cause will be explored using subgroup analysis (described in ***Section 6.5.4***).

To complement Tau^2 and I^2, prediction intervals (PIs) will also be generated to investigate between-study variability.[58] PIs provide a range within which the true treatment effect of a future study is likely to fall, assuming the same conditions as for the included studies.[58] PIs will be generated where random-effects meta-analyses are conducted, and presented as part of its results.[58] PIs will be generated for meta-analyses with 5 or more studies and no clear funnel plot asymmetry is detected.[58]

6.5.3 Small study effects

The presence of small study effects will be assessed using contour-enhanced funnel plot to assess asymmetry for outcomes with a minimum of 10 studies.[58,79]

6.5.4 Subgroup and sensitivity analysis

A priori subgroup and sensitivity analysis will be used to investigate possible causes of clinical, methodological and statistical heterogeneity in meta-analyses due to effect modifiers (e.g. dose, RoB). Subgrouping will be used to explore potential effect modifiers that may lead to differences between comparative studies.[58] The subgroup analyses will use random effects models with the assumption of a normal distribution. A two-tailed Z-test will be used to determine if the difference between the 2 groups is statistically significant. The difference between subgroups will be considered statistically significant if <5% of difference occurs by chance alone (i.e. $p < 0.05$). If there are only 10 trials in the subgroup analyses, Tau^2 will be calculated using trials in both subgroups. If the subgroup analyses includes more than 10 trials, a separate Tau^2 will be calculated for each individual subgroup. *A priori* subgroups of potential effect modifiers will include:

- indication, specifically for muscle cramps (e.g. nocturnal, idiopathic, pregnancy-associated, exercise-associated, liver and cirrhosis-associated)
- age (≥4 years—<18 years, ≥18 years)
- magnesium dosage (based on the standard doses of the listed magnesium supplements on Swissmedic [i.e. <300 mg/ day, ≥300—600 mg/ day])
- magnesium treatment duration (muscle cramps: <60 days, ≥60 days;[4,64,80] calcium oxalate urolithiasis: <6 months, ≥6—12 months, >12 months[78,81])
- per magnesium compound (i.e. magnesium citrate, magnesium aspartate, magnesium oxide)
- Magnesium status as reported in included studies (i.e. patients with hypomagnesemia excluded vs. magnesium status not reported)

Sensitivity analyses will be conducted to investigate the impact of methodological factors on the reported results of the clinical evaluation for both RCTs and NRSIs (separately). Of particular interest is how the conclusions may be affected by RCTs and NRSIs with a high/critical RoB. During this stage, studies assessed as having a high/critical RoB will be excluded, with analyses rerun.

6.5.5 Imputation methods for dealing with missing values

Missing SDs will be obtained from available means, sample sizes, SEs and 95% CIs using formulae detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5).[58] In situations where data are unavailable to calculate SD, it will be imputed using the 'impute_SD' function in the R (version 1.4) package 'metagear', following the imputation methods described by Braken et al, 1992.[75,76,82,83] Where continuous values need to be combined, formulae detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5) will be used.[58] For studies that report outcomes graphically, WebPlotDigitizer will be used to convert graph points to numerical values.[69]

6.5.6 Narrative synthesis

If fewer than 2 comparative studies report an outcome, meta-analysis will be impossible. In such cases, the results will be tabulated and described narratively. For continuous outcomes, SD and change scores (ANCOVA-adjusted), mean change from baseline, or baseline and final follow-up score will be reported for each study arm, along with MDs and 95% CIs comparing the mean effects between groups. For dichotomous outcomes, event rates for each trial arm will be reported along with RR or OR, and 95% CIs comparing the event rates between groups.

6.5.7 Summary of findings

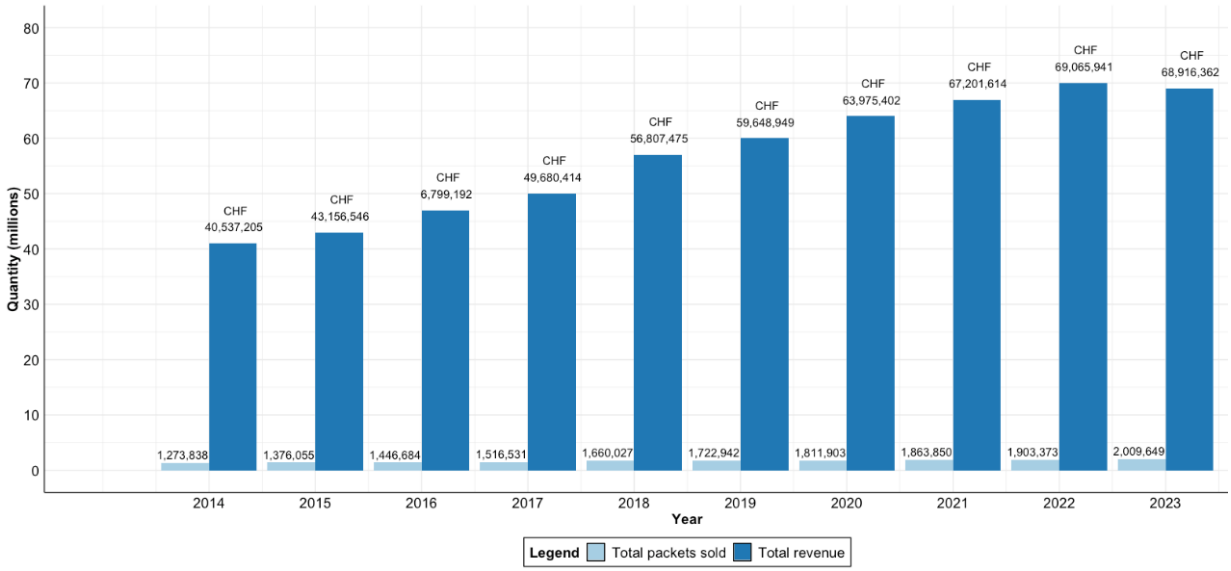
Separate GRADE 'summary of findings' tables will be created for each population of interest, with separate tables for each comparator and study design (RCTs and NRSIs). The outcome-specific certainty will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[73] Results of the assessments for each domain (i.e. risk of bias, inconsistency, indirectness, imprecision, publication bias) will be compiled into an overall evaluation of the certainty of the evidence (i.e. overall GRADE rating), ranging from high to very low.

7 Budget impact assessment

7.1 Current use of oral magnesium

Oral magnesium (ATC code A12CC) is reimbursed via mandatory health insurance. Data provided by © COGE GmbH Tarifpool © SASIS AG shows past utilisation data across Switzerland for reimbursed oral magnesium products (***Figure 1***).

Figure 1 Utilisation of oral magnesium products on the Spezialitätenliste, 2014–2023



Abbreviations: CHF = Swiss franc
Source: Compiled by the authors using Tarifpool. © SASIS AG data prepared by © COGE GmbH.

7.2 Aims of the assessment

The HTA will firstly seek to define who is being prescribed oral magnesium and/or who is claiming oral magnesium in Switzerland. This will include assessing the demographic characteristics and indications for use in patients treated with oral magnesium. If feasible, magnesium use for all licensed indications of relevance to the policy question (i.e. patients without proven hypomagnesaemia, excluding use in primary prevention) will be quantified.

Secondly, the HTA will seek to evaluate the budget impact of oral magnesium treatment for the listed indications (i.e. muscle cramps, urolithiasis [without proven hypomagnesaemia]) under current policy/practice conditions. Proposed methods for estimating use in these patient groups are detailed below.

Finally, the HTA may seek to define the financial implications of certain policy changes in relation to the included indications. The appropriateness of evaluating the potential financial implications of any policy changes will be determined by the findings of the clinical evaluation. If performed, these analyses would assess the change in magnesium use resulting from the policy change, as well as any changes in use of other healthcare resources (e.g. associated healthcare services, comparator services, resources consumed in managing related health consequences), to estimate the net financial impact to the healthcare payer.

Key considerations for the budget impact assessment are outlined below. Methods will be finalised during the HTA.

7.3 Key considerations

7.3.1 Perspective

The budget impact assessment will be performed from the perspective of the statutory health insurance system, focusing solely on the direct medical costs of services covered by Swiss mandatory health insurance. Only services principally reimbursable by the statutory health insurance, irrespective of actual payer, will be included; patient out-of-pocket costs (including over-the-counter costs) for non-reimbursed services will not be considered.

7.3.2 Time horizon

The budget impact assessment will be performed over a time horizon of 5 years.

7.3.3 Demographics and profile of magnesium users

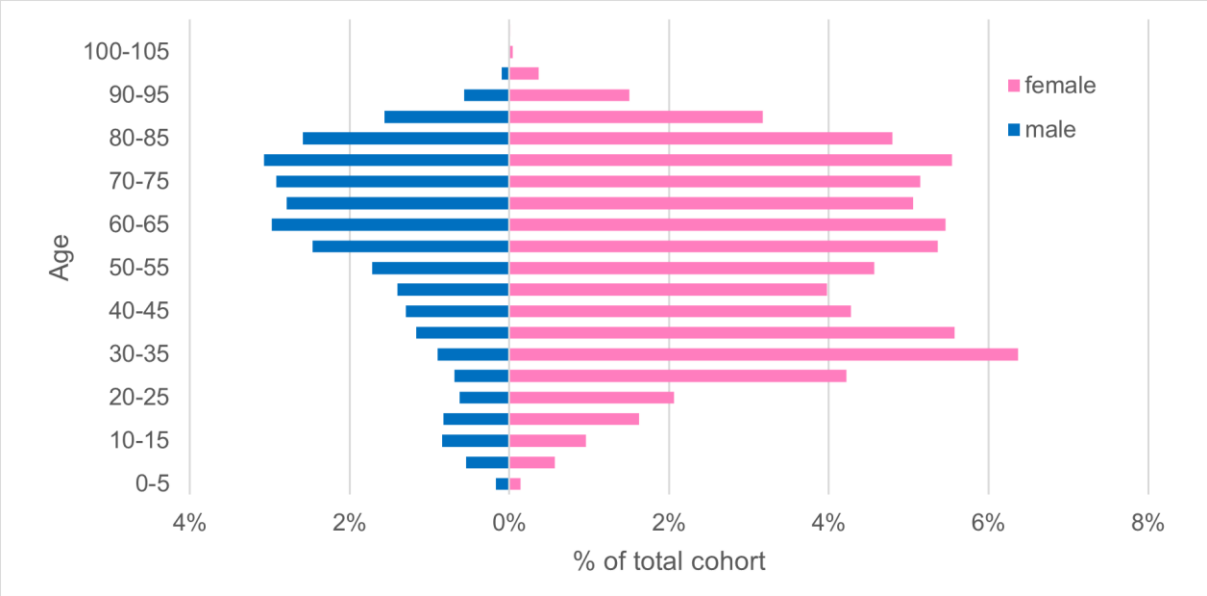
Market data are available on the overall utilisation of oral magnesium reimbursed via mandatory health insurance (***Figure 1***). Frequency of use data (i.e. average claims per person per year) are available from a Swiss insurer database and could be used to estimate the number of patients reflected in the utilisation data.

Demographic characteristics data (age, gender) of patients who claim oral magnesium for any reason are available from a Swiss insurer database (2024 data presented in

Figure 2). Indication data were not available from this source.

It is noted that the available magnesium utilisation data include usage outside the included indications, including in patients with manifest hypomagnesaemia, or conditions or treatments putting them at risk of hypomagnesaemia, as well as any off-label use occurring in practice.

Figure 2 Age and gender distribution of oral magnesium users based on claims data, 2024



Note: Inclusive of all claims data (not specific to indications included in the HTA); inclusive of all patients who made a claim (may include cases were the claim was not reimbursed).
Source: Compiled by the authors using claims data provided by a Swiss insurer.

Based on Swiss clinical expert consultation (see ***Appendix 11.3*** and ***Appendix 11.4***), where advice has been given that oral magnesium is not prescribed in specialist practice, uptake is presumably low for the excluded licensed indications. There are uncertainties in this assumption given it is based on interviews with specialists and may not capture utilisation within general practice. Ideally, diagnosis data is needed to validate this assumption. A healthcare data and analytics company is being consulted in the hope that it may be able to provide further information on diagnoses for which oral magnesium is prescribed.

7.3.4 Size of target populations

Estimates of the size of each target population will be needed for the budget impact assessment. The preferred method is to extrapolate diagnosis data (requested from a healthcare data and analytics company) to estimate the proportion of prescriptions written for the indications of interest (muscle cramps; urolithiasis) across Switzerland. If these data are unavailable, the size of the target populations and uptake among these populations, would instead be estimated using a combination of epidemiological estimates and clinical expert advice.

7.3.5 Scenarios to be modelled

The potential scenarios for consideration will be decided during the HTA. Only policy changes relating to indications within the scope of the current HTA will be considered.

Restricting oral magnesium use to the indications of muscle cramps and urolithiasis could impact the number of patients prescribed oral magnesium in Switzerland. If such a scenario was considered appropriate, analyses would be undertaken to estimate the reduction in oral magnesium

use over a 5-year time horizon and the associated cost savings. These analyses would also model how such restrictions would impact the use of other healthcare resources, including those associated with comparator products, to estimate the net financial impact to the healthcare payer. This modelling would be undertaken only if supported by the clinical findings.

7.3.6 Reporting and uncertainty analysis

All major assumptions, input parameters and data sources. Scenario analyses will be used to explore the impact of certain assumptions on the results, while a one-way sensitivity analysis will be undertaken to identify key drivers of the analyses.

8 Ethical, legal, social and organisational issues

8.1 Databases and search strategy

The systematic literature searches detailed in ***Section 6.1***, including search strings and relevant data sources, will be used to identify studies that investigate ethical, legal, social and organisational issues related to magnesium supplementation. In addition, reference lists from included studies will be screened for relevant citations. Targeted, non-systematic keyword searches may be conducted to supplement the results of the systematic literature searches if, for example, broader issues relating to magnesium are discovered that may have been insufficiently captured by the systematic search strategy.

8.2 Inclusion/exclusion criteria and study selection

The inclusion and exclusion criteria (***Section 6.2***) will be applied to the selection of studies reporting on ethical, legal, social and organisational domains, noting that a broader selection of study designs will be eligible for inclusion for these domains. Systematic reviews, narrative literature reviews, RCTs, NRSIs, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies will be considered for inclusion. All studies will be screened using the study selection process described in ***Section 6.2***.

8.3 Data extraction, analysis and synthesis

Data will be extracted from studies for publication year, study design, sample size (where relevant) and key findings, by one reviewer and double checked by a second reviewer. If disagreements between reviewers arise, a third reviewer will confirm the extraction. Study design characteristics and key findings from included studies will be presented in tables and described narratively. Results relating to ethical issues will be synthesised according to a normative principlist framework, addressing issues of autonomy, non-maleficence, beneficence and justice.[84] The results for other domains will be tabulated and discussed narratively, synthesising key themes presented in the literature.

9 Summary and Outlook

9.1 Summary

The proposed HTA will separately evaluate the safety, efficacy/effectiveness and budget impact of oral magnesium in patients aged ≥4 years with muscle or leg cramps without proven hypomagnesaemia, and in patients aged ≥4 years with prior calcium oxalate urolithiasis without proven hypomagnesaemia for secondary prevention of stone recurrence.

A systematic literature search will be conducted for the clinical evaluation, considering RCTs in the first instance, and NRSI evidence to fill gaps in the RCT evidence base. Where there are more than 2 comparative studies reporting on an outcome of interest in the same population against the same comparator, meta-analyses will be conducted. Where outcomes cannot be meta-analysed, the results will be tabulated and described narratively. Based on preliminary scoping searches, it is expected that sufficient RCT evidence will be available to evaluate the use of magnesium supplements for treating cramps, but potentially not for treating calcium oxalate stones. It appears likely that NRSI evidence will need to be sourced for this indication.

A budget impact analysis will be conducted. The analysis will project costs to the payer over 5 years using selected current and possible future policy and pricing scenarios. Utilisation data for reimbursed oral magnesium products are available, but more specific data are needed to assess use for the target indications. The accuracy of the budget impact assessment depends on sourcing reliable data for the relevant populations. While various data sources are being explored, uncertainty remains regarding the availability for this HTA.

Literature relating to ethical, legal, social and organisational issues of magnesium supplementation will be identified via systematic searches, targeted keyword searches and pearling reference lists of included studies. The results of included studies will be tabulated and synthesised narratively.

9.2 Project-related challenges

A key challenge in the development of this protocol was refining the scope of the proposed HTA to focus on the most relevant indications, because oral magnesium is currently licensed for a variety of conditions in Switzerland, including cardiovascular tachyarrhythmia, coronary heart disease, (pre-) eclampsia, tocolysis, tetanic syndrome, neuromuscular hyperexcitability, muscle cramps and prevention of recurrent calcium oxalate urolithiasis.

To understand the current role and relevance of oral magnesium for the licensed indications in Swiss clinical practice, Swiss clinical experts and relevant CPGs were consulted as part of the protocol development and refinement of the PICO criteria. As a result, the proposed HTA will separately evaluate the safety, efficacy/effectiveness and budget impact of oral magnesium compared to placebo, no treatment or standard of care in patients aged ≥4 years with muscle or leg cramps and without proven hypomagnesaemia, and in patients aged ≥4 years with prior calcium

oxalate urolithiasis for secondary prevention of stone recurrence and without proven hypomagnesaemia.

Defining the current use of oral magnesium for each licensed indication remains a key challenge. While utilisation data are available, it seems unlikely that reliable indication-specific data will be available for this HTA. In the absence of market data, an epidemiological approach is proposed as an alternative for the included indications.

9.3 Outlook

The HTA protocol precedes production of an HTA report, comprising a focused assessment of various aspects of the health technology in question, presenting the applied analytic methods, their execution and the results. The analytical process is comparative, systematic and transparent. The external review group consulted during the protocol phase is consulted again during the HTA phase. The HTA draft report is subsequently presented to the stakeholders for consultation. Communication with the reviewers and stakeholders is coordinated by the FOPH.

10 References

1. Skolarikos A, Neisius A, Petřík A, et al. EAU guidelines on Urolithiasis: European Association of Urology, 2022.
2. Topka H. Leitlinien für Diagnostik und Therapie in der Neurologie: Crampi/Muskelkrämpfe: Deutsche Gesellschaft für Neurologie, 2023.
3. Garrison SR, Korownyk CS, Kolber MR, et al. Magnesium for skeletal muscle cramps. *Cochrane Database of Systematic Reviews* 2020(9)
4. Barna O, Lohoida P, Holovchenko Y, et al. A randomized, double-blind, placebo-controlled, multicenter study assessing the efficacy of magnesium oxide monohydrate in the treatment of nocturnal leg cramps. *Nutrition Journal* 2021;20(1):90.
5. Gröber U, Schmidt J, Kisters K. Magnesium in Prevention and Therapy. *Nutrients* 2015;7(9):8199-226.
6. de Baaij JHF, Hoenderop JGJ, Bindels RJM. Magnesium in Man: Implications for Health and Disease. *Physiological Reviews* 2015;95(1):1-46.
7. Ross AC, Caballero B, Cousins RJ, et al. Modern nutrition in health and disease: Jones & Bartlett Learning 2020.
8. Gragossian A, Bashir, K., Bhutta, B. S., & Friede, R. Hypomagnesemia: StatPearls Publishing. 2023.
9. Shastri S, Patel J, Sambandam KK, et al. Kidney Stone Pathophysiology, Evaluation and Management: Core Curriculum 2023. *American Journal of Kidney Diseases* 2023;82(5):617-34.
10. Sorokin I, Mamoulakis C, Miyazawa K, et al. Epidemiology of stone disease across the world. *World J Urol* 2017;35(9):1301-20.
11. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. *Nat Rev Dis Primers* 2016;2:16008.
12. Finkielstein VA, Goldfarb DS. Strategies for preventing calcium oxalate stones. *Cmaj* 2006;174(10):1407-9.
13. Hughes P. The CARI guidelines. Kidney stones epidemiology. *Nephrology (Carlton)* 2007;12 Suppl 1:S26-30.
14. Raheem OA, Khandwala YS, Sur RL, et al. Burden of Urolithiasis: Trends in Prevalence, Treatments, and Costs. *European Urology Focus* 2017;3(1):18-26.
15. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int* 2005;68(4):1808-14.
16. Geraghty RM, Cook P, Walker V, et al. Evaluation of the economic burden of kidney stone disease in the UK: a retrospective cohort study with a mean follow-up of 19 years. *BJU International* 2020;125(4):586-94.
17. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Treatment for Kidney Stones: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); 2107 [Available from: https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/treatment accessed 27/09/2024].
18. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diagnosis of kidney stones 2017 [Available from: https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/diagnosis accessed 31/10/2024].
19. Leslie SW, Sajjad H, Bashir K. 24-Hour Urine Testing for Nephrolithiasis: Interpretation and Treatment Guidelines. *StatPearls [Internet]* 2023
20. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. *Nature Reviews Urology* 2016;13(11):654-62.
21. Minetto MA, Holobar A, Botter A, et al. Origin and Development of Muscle Cramps. *Exercise and Sport Sciences Reviews* 2013;41(1):3-10.
22. Stern L, Bernick C. Muscle Cramps. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition ed. Boston: Butterworths 1990.
23. Walker HK, Hall WD, Hurst JW. Clinical methods: the history, physical, and laboratory examinations. 1990
24. Jansen PH, Joosten EM, Van Dijck J, et al. The incidence of muscle cramp. *Journal of Neurology, Neurosurgery & Psychiatry* 1991;54(12):1124.
25. Sohrabvand F, Karimi M. Frequency and predisposing factors of leg cramps in pregnancy: A prospective clinical trial. *Tehran University Medical Journal* 2009;67:661-64.
26. Naylor JR, Young JB. A General Population Survey of Rest Cramps. *Age and Ageing* 1994;23(5):418-20.

27. Kantorowski P, Hiller W, Garrett W, et al. 620 Cramping studies in 2600 endurance athletes. *Medicine & Science in Sports & Exercise* 1990;22(2):S104.
28. Maisonneuve H, Chambe J, Delacour C, et al. Prevalence of cramps in patients over the age of 60 in primary care : a cross sectional study. *BMC Family Practice* 2016;17(1):111.
29. Bordoni B, Sugumar K, Sugumar K, et al. Muscle Cramps: StatPearls Publishing, Treasure Island (FL) 2023.
30. Katzberg H, Sadeghian H. Muscle cramps 2019. https://practicalneurology.com/articles/2019-aug-july/muscle-cramps (accessed 31/10/2024).
31. Katzberg HD, Khan AH, So YT. Assessment: Symptomatic treatment for muscle cramps (an evidence-based review). *Neurology* 2010;74(8):691-96.
32. Blancquaert L, Vervaet C, Derave W. Predicting and Testing Bioavailability of Magnesium Supplements. *Nutrients* 2019;11(7):1663.
33. Schutten JC, Joris PJ, Groendijk I, et al. Effects of Magnesium Citrate, Magnesium Oxide, and Magnesium Sulfate Supplementation on Arterial Stiffness: A Randomized, Double-Blind, Placebo-Controlled Intervention Trial. *Journal of the American Heart Association* 2022;11(6):e021783.
34. Kohri K, Garside J, Blacklock NJ. The role of magnesium in calcium oxalate urolithiasis. *Br J Urol* 1988;61(2):107-15.
35. Hammarsten G. Calcium oxalate and its solubility in the presence of inorganic salts, with special reference ot the occurence of oxalate. *CR Lab Carlsberg* 1929;17:1.
36. Riley JM, Kim H, Averch TD, et al. Effect of magnesium on calcium and oxalate ion binding. *J Endourol* 2013;27(12):1487-92.
37. Sakhaee K, Nicar M, Hill K, et al. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney International* 1983;24(3):348-52.
38. Phillips R, Hanchanale VS, Myatt A, et al. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev* 2015;2015(10):Cd010057.
39. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *The Journal of urology* 2014;192(2):316-24.
40. Anonymous. Magnesium supplementation for use in the treatment of various indications: Questions for nephrology clinical expert, 2024.
41. Bergsland KJ, Worcester EM, Coe FL. Role of proximal tubule in the hypocalciuric response to thiazide of patients with idiopathic hypercalciuria. *Am J Physiol Renal Physiol* 2013;305(4):F592-9.
42. Food and Drug Administration. Drug Products Containing Quinine; Enforcement Action Dates. In: Department of Health and Human Services, ed., 2006.
43. Anonymous. Magnesium supplementation for use in the treatment of various indications: Questions for neurology clinical expert, 2024.
44. Kern A, Grimsby G, Mayo H, et al. Medical and dietary interventions for preventing recurrent urinary stones in children. *Cochrane Database Syst Rev* 2017;11(11):CD011252.
45. Mokhless I, Zahran AR, Youssif M, et al. Factors that predict the spontaneous passage of ureteric stones in children. *Arab J Urol* 2012;10(4):402-7.
46. Guy Peryer, Su Golder, Daniela R Junqueira, et al. Chapter 19: Adverse effects. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane, 2019.
47. Liljeberg E, Andersson A, Blom Malmberg K, et al. High Adherence to Oral Nutrition Supplements Prescribed by Dietitians: A Cross-Sectional Study on Hospital Outpatients. *Nutr Clin Pract* 2019;34(6):887-98.
48. Patrick DL, Erickson P. Health status and health policy: quality of life in health care evaluation and resource allocation. 1993
49. Foster C, Baki J, Nikirk S, et al. Comprehensive Health-State Utilities in Contemporary Patients With Cirrhosis. *Hepatol Commun* 2020;4(6):852-58.
50. Tapper EB, Kanwal F, Asrani SK, et al. Patient-reported outcomes in cirrhosis: a scoping review of the literature. *Hepatology* 2018;67(6):2375-83.
51. Joshi HB, Johnson H, Pietropaolo A, et al. Urinary Stones and Intervention Quality of Life (USIQoL): Development and Validation of a New Core Universal Patient-reported Outcome Measure for Urinary Calculi. *European Urology Focus* 2022;8(1):283-90.
52. Tapper EB, Trivedi H, Simonetto DA, et al. The RELAX randomized controlled trial: Stretching versus meditation for nocturnal muscle cramps. *Liver International* 2024;44(9):2434-41.

53. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33.
54. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
55. Hawke F, Sadler SG, Katzberg HD, et al. Non-drug therapies for the secondary prevention of lower limb muscle cramps. *Cochrane Database of Systematic Reviews* 2021(5)
56. Rabbitt L, Mulkerrin EC, O'Keeffe ST. A review of nocturnal leg cramps in older people. *Age and Ageing* 2016;45(6):776-82.
57. Sebo P, Haller DM, Kaiser C, et al. Health-related quality of life associated with nocturnal leg cramps in primary care: a mixed methods study. *Family Practice* 2022;39(1):85-91.
58. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5: Cochrane; 2024 [Available from: www.training.cochrane.org/handbook accessed September 2024].
59. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;4(1):1.
60. Azarfar A, Esmaeili M, Tousi N, et al. Evaluation of the effects of magnesium supplement in primary and secondary preventions of nephrolithiasis: a systematic review. *Reviews in Clinical Medicine* 2016;3(1):18-22.
61. Lo C, Khor Q, Abdullatif V, et al. Systematic review of pharmacological, complementary and alternative therapies for the prevention of calcium oxalate stones. *Asian Journal of Urology* 2024
62. Phillips R, Hanchanale VS, Myatt A, et al. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database of Systematic Reviews* 2015(10)
63. Liu J, Song G, Zhao G, et al. Effect of oral magnesium supplementation for relieving leg cramps during pregnancy: A meta-analysis of randomized controlled trials. *Taiwanese Journal of Obstetrics and Gynecology* 2021;60:609-14.
64. Sebo P, Cerutti B, Haller D. Effect of magnesium therapy on nocturnal leg cramps: A systematic review of randomized controlled trials with meta-analysis using simulations. *Family practice* 2013;31
65. Souza ACR, Vasconcelos AR, Dias DD, et al. The Integral Role of Magnesium in Muscle Integrity and Aging: A Comprehensive Review. *Nutrients* 2023;15(24):5127.
66. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. *Systematic reviews* 2016;5:1-10.
67. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J* 2012;5(Suppl 1):i3-i14.
68. Cuello-Garcia CA, Santesso N, Morgan RL, et al. GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. *Journal of Clinical Epidemiology* 2022;142:200-08.
69. Ankit Rohatgi. WebPlotDigitizer: Ankit Rohatgi; 2020 [Available from: https://automeris.io/WebPlotDigitizer/ accessed September 2024].
70. Sterne J, Savović J, Page M, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366
71. Sterne J, Higgins J. The Risk Of Bias In Non-randomized Studies – of Interventions, Version 2 (ROBINS-I V2) 2024 [Available from: https://www.riskofbias.info/welcome/robins-i-v2].
72. GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. *McMaster University and Evidence Prime* 2025
73. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-94.
74. Schunemann H, Brozek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations (The GRADE Working Group): http://gdt. guidelinedevelopment. org/app/handbook/handbook. html, 2013.
75. RStudio Team. RStudio: Integrated Development for R. Boston, USA: RStudio, 2020.
76. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: Foundation for Statistical Computing, 2020.
77. Veroniki AA, McKenzie JE. A brief note on the common (fixed)-effect meta-analysis model. *Journal of Clinical Epidemiology* 2024;169
78. Melnick I, Landes RR, Hoffman AA, et al. Magnesium therapy for recurring calcium oxalate urinary calculi. *J Urol* 1971;105(1):119-22.
79. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *Journal of Clinical Epidemiology* 2008;61(10):991-96.

80. Kaufman N, White D, Bull J, et al. Does Magnesium Supplementation Treat Nocturnal Leg Cramps? *Am Fam Physician* 2023;108(6):619-20.
81. Reddy SV, Shaik AB, Bokkisam S. Effect of potassium magnesium citrate and vitamin B-6 prophylaxis for recurrent and multiple calcium oxalate and phosphate urolithiasis. *Korean J Urol* 2014;55(6):411-6.
82. Lajeunesse MJ. Facilitating systematic reviews, data extraction and meta-analysis with the metagear package for r. *Methods in Ecology and Evolution* 2016;7(3):323-30.
83. Bracken M. Statistical methods for analysis of effects of treatment in overviews of randomized trials. *Effective care of the newborn infant* 1992:13-20.
84. Quante M, Vieth A. Defending principlism well understood. *J Med Philos* 2002;27(6):621-49.
85. INAHTA. INAHTA MEMBERS LIST 2024 [Available from: https://www.inahta.org/members/members_list/].
86. Zeppenfeld K, Tfelt-Hansen J, De Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). *European heart journal* 2022;43(40):3997-4126.
87. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2016;133(14):e506-e74.
88. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;149(1):e1-e156.
89. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. *Canadian Journal of Cardiology* 2020;36(12):1847-948.
90. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2023;82(9):833-955.
91. Agency for Clinical Innovation. Management of Threatened Preterm Labour: NSW Health 2022.
92. World Health Organization. WHO recommendation on tocolytic therapy for improving preterm birth outcomes: World Health Organization, 2022.
93. National Institute for Health and Care Excellence. Preterm labour and birth National Institute for Health and Care Excellence, 2015.
94. Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG), Hösli I, Sperschneider C, et al. Expertenbrief No 41: Tokolyse bei vorzeitiger Wehentätigkeit, 2013.
95. Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG), Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Oesterreichische Gesellschaft fur Gynakologie und Geburtshilfe (OEGGG). Prävention und Therapie der Frühgeburt, 2022.
96. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management: National Institute for Health and Care Excellence, 2019.
97. Queensland Clinical Guidelines. Hypertension and pregnancy Queensland Health, , 2021.
98. German Society for Obstetrics And Gynecology (DGGG). Hypertensive Erkrankungen in der Schwangerschaft (HES): Diagnostik und Therapie: German Society for Obstetrics And Gynecology (DGGG), , 2024.
99. De Wel B, Claeys KG. Neuromuscular hyperexcitability syndromes. *Current Opinion in Neurology* 2021;34(5):714-20.
100. Heidbreder A, Trenkwalder C. Leitlinien für Diagnostik und Therapie in der Neurologie: Restless Legs Syndrome: Deutschen Gesellschaft für Neurologie (DGN) und der Deutschen
Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), 2022.
101. Nanayakkara B, Di Michiel J, Yee B. Restless legs syndrome. *Australian Journal for General Practitioners* 2023;52:615-21.
102. Silber MH, Buchfuhrer MJ, Earley CJ, et al. The Management of Restless Legs Syndrome: An Updated Algorithm. *Mayo Clinic Proceedings* 2021;96(7):1921-37.

103. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2016;87(24):2585-93.
104. NHS GH, NHS Foundation Trust,. Treatment Guideline: Acute treatmenr of hypocalcaemia (adults), 2021.
105. Barcelo P, Wuhl O, Servitge E, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993;150(6):1761-4.
106. Cicerello E, Merlo F, Gambaro G, et al. Effect of alkaline citrate therapy on clearance of residual renal stone fragments after extracorporeal shock wave lithotripsy in sterile calcium and infection nephrolithiasis patients. *J Urol* 1994;151(1):5-9.
107. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997;158(6):2069-73.
108. Liebman M, Costa G. Effects of calcium and magnesium on urinary oxalate excretion after oxalate loads. *J Urol* 2000;163(5):1565-9.
109. Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. *Rev Urol* 2003;5(4):227-31.
110. Fontenelle LF, Sarti TD. Kidney Stones: Treatment and Prevention. *Am Fam Physician* 2019;99(8):490-96.
111. Roguin Maor N, Alperin M, Shturman E, et al. Effect of Magnesium Oxide Supplementation on Nocturnal Leg Cramps: A Randomized Clinical Trial. *JAMA Intern Med* 2017;177(5):617-23.
112. Barbagallo M, Veronese N, Dominguez LJ. Magnesium in Aging, Health and Diseases. *Nutrients* 2021; 13(2).
113. Nygaard IH, Valbø A, Pethick SV, et al. Does oral magnesium substitution relieve pregnancy-induced leg cramps? *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2008;141(1):23-26.
114. Veronese N, Berton L, Carraro S, et al. Effect of oral magnesium supplementation on physical performance in healthy elderly women involved in a weekly exercise program: a randomized controlled trial1,2,3. *The American Journal of Clinical Nutrition* 2014;100(3):974-81.
115. Dahle LO, Berg G, Hammar M, et al. The effect of oral magnesium substitution on pregnancy-induced leg cramps. *American Journal of Obstetrics and Gynecology* 1995;173(1):175-80.

11 Appendices

11.1 Search strategy

Table 3 Search strategy – Ovid (Medline + Embase)

PICO domain	#	Search term
Population 1 (calcium oxalate urolithiasis)	1	Exp Urolithiasis/
	2	Urolithiasis.ab,ti.
	3	Lithiasis.ab,ti.
	4	Nephrolithiasis.ab,ti.
	5	Calculi.ab,ti.
	6	Stone.ab,ti.
	7	1 or 2 or 3 or 4 or 5 or 6
	8	Calcium oxalate/
	9	Calcium oxalate.ab,ti.
	10	8 or 9
	11	7 and 10
Population 2 (muscle cramps)	12	Muscle cramp/
	13	Cramp*.ab,ti.
	14	Muscle contraction*.ab,ti.
	15	Muscle spasm*.ab,ti.
	16	12 or 13 or 14 or 15
Intervention	17	Exp Magnesium Compounds/
	18	Magnesium.ab,ti.
	19	17 or 18
Combined search	20	**(11 or 16) and 19**
Limit: Humans	21	exp Animals/
	22	exp Humans/
	23	21 and 22
	24	21 not 23
	25	20 not 24
Limit: Language	26	English.lg.
	27	French.lg.
	28	German.lg.
	29	Italian.lg.

	30	26 or 27 or 28 or 29
	31	25 and 30
Limit: Publication type	32	Editorial.pt.
	33	Letter.pt.
	34	Congress.pt.
	35	Conference abstract.pt.
	36	Conference paper.pt.
	37	Conference review.pt.
	38	Case Reports.pt.
	39	Clinical conference.pt.
	40	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
	41	31 not 40
Deduplicate Medline + Embase	**42**	**Deduplicate**

Table 4 Search strategy – Cochrane Library

PICO Domain	#	Search term
Intervention terms	1	Magnesium
Population terms	2	Cramps
	3	Kidney stones
	4	Urolithiasis
	5	Nephrolithiasis
Combined search	**6**	**1 AND (2 OR 3 OR 4 OR 5)**

Table 5 Search strategy – INAHTA database

PICO Domain	#	Search term
Intervention terms	1	Magnesium
Population terms	2	Cramps
	3	Kidney stones
	4	Urolithiasis
Combined search	**5**	**1 AND (2 OR 3 OR 4)**

Table 6 Search strategy – Clinicaltrials.gov

PICO Domain	#	Search term
Intervention terms	1	Magnesium
Population terms	2	Cramp*
	3	Urolithiasis
Combined search	**4**	**1 AND (2 OR 3)**

Table 7 Search strategy – EU Clinical trials registry

PICO Domain	#	Search term
Intervention terms	1	Magnesium
Population terms	2	Cramp*
	3	Kidney stone*
Combined search	**4**	**1 AND (2 OR 3)**

Table 8 HTA agency websites

HTA Websites	
Global	
INAHTA HTA Database	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net

Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es

Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html

Source: Based on INAHTA members list[85]

11.2 Licensed indications of oral magnesium preparations reimbursed by the Swiss mandatory health insurance (as listed on Swissmedic)

Table 9 Full list of licensed indications for magnesium preparations approved by Swissmedic

Trade name	Indications	
	German	English
Magnesiocard® Filmtabletten/ Brausetabletten/ Granulat	Therapie des Magnesium-Mangels, verursacht durch z.B. Fehlernährung, Diuretika-oder andere medikamentöse Therapien, Diarrhö, Alkoholabusus; tachykarde Herzrhythmusstörungen, vor allem bei Resistenz gegenüber anderen Antiarrhythmika; Adjuvans zu Beta-2-Tokolytika bei Prodromi frühzeitiger Geburt resp. drohendem Spätabort; zur Deckung eines erhöhten Bedarfs im Hochleistungssport und während der Schwangerschaft; Therapie der Eklampsie, Präeklampsie und des tetanischen Syndroms; Wadenkrämpfe, Muskelzuckungen, Restless Legs.	Treatment of magnesium deficiency caused by, for example, malnutrition, diuretic or other drug therapies, diarrhoea, alcohol abuse; tachycardic cardiac arrhythmias, especially in cases of resistance to other antiarrhythmic drugs; adjuvant to beta-2-tocolytics in prodromes of premature birth or threatened late abortion; to meet increased needs in high-performance sports and during pregnancy; treatment of eclampsia, preeclampsia and tetanic syndrome; calf cramps, muscle twitches, restless legs.
Magnesium Sandoz®	Zur Deckung eines erhöhten Bedarfs an Magnesium im Hochleistungssport und während der Schwangerschaft und Stillzeit; Bei magnesiumarmer Ernährung, bei Wadenkrämpfen; Auf ärztliche Verordnung oder auf Rat eines Apothekers: Magnesium-Mangel bei Malabsorption, erhöhten intestinalen und/oder renalen Verlusten (z.B. Diuretikatherapie); Neuromuskuläre Übererregbarkeit, tetanisches Syndrom, muskuläre Krampfzustände; Präeklampsie. Eklampsie. Als Zusatztherapie zur Tokolyse mit β2-Adrenergika; Bei tachykarden Herzrhythmusstörungen, v.a. bei Resistenz gegenüber anderen Antiarrhythmika.	To cover an increased need for magnesium in high-performance sports and during pregnancy and breastfeeding; in case of a diet low in magnesium, in case of calf cramps; on medical prescription or on the advice of a pharmacist; magnesium deficiency due to malabsorption, increased intestinal and/or renal losses (e.g. diuretic therapy); neuromuscular hyperexcitability, tetanic syndrome, muscular spasms; preeclampsia, eclampsia; as additional therapy to tocolysis with β_2-adrenergics; in tachycardic cardiac arrhythmias, especially in cases of resistance to other antiarrhythmics.
Mg5-Granoral®/ Mg5-Longoral®/ Mg5-Oraleff®	Deckung eines erhöhten Bedarfes (z.B. Wachstum, Hochleistungssport, Schwangerschaft, Stillzeit); Magnesiumarme Ernährung; Wadenkrämpfe. Auf ärztliche Verordnung oder auf Rat eines Apothekers: Neuromuskuläre Störungen wegen Magnesiummangel, muskuläre Krämpfe. Auf ärztliche Verordnung: Bei tachykarden Herzrhythmusstörungen (Tachykardie), v.a. bei Resistenz gegenüber anderen Antiarrhythmika; Adjuvans zu β2-Adrenergika bei Prodromi frühzeitiger Geburt bzw. drohendem Spätabort; Behandlung der Eklampsie, Pre-Eklampsie und des tetanischen Syndroms; Enterale oder renale Magnesiumverluste (chronische Diarrhoe, Diuretikatherapie).	Covering increased needs (e.g. growth, high-performance sports, pregnancy, breastfeeding); low-magnesium diet; calf cramps; on prescription or on the advice of a pharmacist; neuromuscular disorders due to magnesium deficiency, muscular cramps; on doctor's prescription in case of tachycardic cardiac arrhythmias (tachycardia), especially in case of resistance to other antiarrhythmic drugs; adjuvant to β2-adrenergics in prodromes of preterm birth or threatened late abortion; treatment of eclampsia, pre-eclampsia and tetanic syndrome; enteral or renal magnesium losses (chronic diarrhoea, diuretic therapy).
Magnesium-Diasporal® Citracaps/ Magnesium-Diasporal®* Granulat	Prophylaxe und Therapie tachykarder Herzrhythmusstörungen, Begleitmedikation bei koronarer Herzkrankheit; Neuromuskuläre Übererregbarkeit, tetanisches Syndrom, muskuläre Krampfzustände, Wadenkrämpfe; Myositis ossificans; Rezidivprophylaxe der Calcium-Oxalat-Urolithiasis; Präeklampsie, Eklampsie; Magnesiummangelzustände; zur Deckung eines erhöhten Bedarfs bei Hochleistungssport, in der Schwangerschaft und Stillzeit; Therapiebedingter Magnesiummehrbedarf: Bei Diuretika-, Aminoglycosid-, Cyclosporin A-, Amphotericin B-Therapie und Digitalisüberempfindlichkeit.	Prophylaxis and treatment of tachycardic cardiac arrhythmias, concomitant medication in coronary heart disease; neuromuscular hyperexcitability, tetanic syndrome, muscular spasms, calf cramps; myositis ossificans; recurrence prevention of calcium oxalate urolithiasis; preeclampsia, eclampsia; magnesium deficiency states; to cover increased needs in high-performance sports, during pregnancy and breastfeeding; therapy-related increased magnesium requirement in diuretic, aminoglycoside, cyclosporin A, amphotericin B therapy and digitalis hypersensitivity.

AndreaMag®/ Solmag 300®	Magnesiummangel infolge ungenügender Zufuhr, infolge Malabsorption, erhöhter intestinaler und/oder renaler Ausscheidung (chronische Diarrhö, Laxantienabusus, Interaktionen mit bestimmten anderen Medikamenten); Zur Deckung eines erhöhten Bedarfs im Hochleistungssport, während der Schwangerschaft und der Stillzeit; Auf ärztliche Verordnung oder auf Rat eines Apothekers: Neuromuskuläre Übererregbarkeit, muskuläre Krampfzustände, Wadenkrämpfe; Rezidivprophylaxe der Calcium-Oxalat-Urolithiasis; Therapiebedingter Magnesiummehrbedarf: Bei Diuretika-, Aminoglycosid-, Cyclosporin A-, Amphotericin B-Therapie und Digitalisüberempfindlichkeit; Auf ärztliche Verordnung: Tachykarde Herzrhythmusstörungen, namentlich solche, die gegenüber anderen Antiarrhythmika resistent sind; Begleitmedikation bei koronarer Herzkrankheit; Tetanisches Syndrom; Präeklampsie, Eklampsie; Adjuvant zu β2-Tokolytika bei Prodromi frühzeitiger Geburt resp. drohendem Spätabort.	Magnesium deficiency due to insufficient intake, malabsorption, increased intestinal and/or renal excretion (chronic diarrhoea, laxative abuse, interactions with certain other medications); to meet increased needs in high-performance sports, during pregnancy and breastfeeding; on prescription or on the advice of a pharmacist: neuromuscular hyperexcitability, muscular spasms, calf cramps; recurrence prevention of calcium oxalate urolithiasis; therapy-related increased magnesium requirement in diuretic, aminoglycoside, cyclosporin A, amphotericin B therapy and digitalis hypersensitivity; on doctor's prescription: tachycardic cardiac arrhythmias, particularly those resistant to other antiarrhythmic drugs; concomitant medication for coronary heart disease; tetanic syndrome; preeclampsia, eclampsia; adjuvant to β_2-tocolytics in prodromes of preterm birth or threatened late abortion.

Notes: * Also available as preparation without sugar (zuckerfrei).

Table 10 Licensed indications of specific magnesium supplements reimbursed by Swiss mandatory health insurance

Trade name; Brand	Dosage/ Formulation	Package details	Active ingredient/ compound	Approved indications										
				CT	CAD	(P)EC	TOC	TS	NH	MC	MT	RL	KS	O
Magnesiocard®[a]; Biomed AG	2.5 mmol (60.8 mg) film-coated tablet	100 pack	Magnesium aspartate hydrochloride trihydrate	X[b]		X	X[c]	X		X[d]	X	X		X
	7.5 mmol (182.3 mg) effervescent tablet	20 pack												
		60 pack												
	5 mmol (121.5 mg) granules	20 sachets												
		50 sachets												
	10 mmol (243 mg) granules	20 sachets												
		50 sachets												
Magnesium Sandoz®; Sandoz Pharma AG	10 mmol (243 mg) effervescent tablet	20 pack	Magnesium aspartate dihydrate and magnesium citrate	X[b]		X	X[e]	X	X	X[f]				X
		40 pack												
Mg5-Granoral®; OM Pharma Suisse SA	12 mmol (292 mg) granules	10 sachets	Magnesium aspartate dihydrate	X[b]		X	X[c]	X		X[f]				X
		30 sachets												
Mg5-Longoral®; OM Pharma Suisse SA	5 mmol (121.5 mg) chewable tablet	20 pack	Magnesium aspartate tetrahydrate	X[b]		X	X[c]	X		X				X
		50 pack												
		100 pack												
Mg5-Oraleff®; OM Pharma Suisse SA	7.5 mmol (182.3 mg) effervescent tablet	30 pack	Magnesium aspartate dihydrate	X[b]		X	X[c]	X		X[f]				X
		60 pack												
Magnesium-Diasporal® Citracaps; Doetsch Grether AG	4 mmol (100 mg) capsule	120 pack	Magnesium citrate	X[g]	X[e]	X		X	X	X[f]			X[h]	X
Magnesium-Diasporal®[i] Granulat; Doetsch Grether AG	12.4 mmol (300 mg) granules (also available sugar-free)	20 sachets	Magnesium citrate anhydrous	X[g]	X[e]	X		X	X	X[f]			X[h]	X
		50 sachets												
AndreaMag®; Andreabal AG	12.3 mmol (300 mg) effervescent tablet	20 pack	Light magnesium oxide	X[b]	X[e]	X	X[c]	X	X	X[f]			X[h]	X
		60 pack												
Solmag 300®; Nutrimed AG	12.3 mmol (300 mg) effervescent tablet	20 pack	Light magnesium oxide	X[b]	X[e]	X	X[c]	X	X	X[f]			X[h]	X
		60 pack												

Abbreviations: CAD = coronary artery disease; **CT** = cardiac tachyarrhythmias; **KS** = kidney stones; **MC** = muscle cramps; **MT** = muscular twitches; **NH** = neuromuscular hyperexcitability; **O** = other; **RL** = restless legs; **TOC** = tocolysis; **TS** = tetanic syndrome; **(P)EC** = (pre-) eclampsia.

Notes:

[a] Per the Spezialitätenliste, Magnesiocard® also available in injectable intravenous (IV) solution and concentrate for preparation of IV solution. These formulations are outside the scope of this HTA protocol.

[b] Especially indicated in the case of resistance to treatment with other antiarrhythmic drugs

[c] Adjuvant to beta 2-tocolytics in case of prodrome symptoms of premature birth or threat of a late abortion

[d] Cramps of the calf

[e] As an adjuvant treatment

[f] Muscle cramps and cramps of the calves

[g] Prophylaxis and treatment

[h] Prevention of recurrences

[i] Also available as preparation without sugar (Zuckerfrei)

11.3 Overview of the recommended use of oral magnesium in the licensed indications

Table 11 Recommended use of oral magnesium in the licensed indications per CPGs and clinical expert consultation

Indication	Oral magnesium recommended by CPGs	Oral magnesium recommended by clinical expert(s)	Final inclusion/ exclusion decision*
Included indications			
Muscle cramps	☑	☑	☑
Calcium oxalate urolithiasis	☑	☑	☑
Excluded indications			
Cardiac tachyarrhythmias	☒	☒	☒
Coronary heart disease	☒	☒	☒
Impending late abortion or prodrome of early delivery	☒	☑	☒
(Pre-) eclampsia	☒	☒	☒
Neuromuscular hyperexcitability and muscle twitches	☒	☒	☒
Restless leg syndrome	☒	☑	☒
Tetanic syndrome	☒	☒	☒

Abbreviations: CPG = clinical practice guideline.

Legend: ☑ = yes; ☒ = no.

Notes: * Rationale for the excluded indications is provided in ***Appendix 11.4***.

11.4 Rationale for excluded indications

During the production of this HTA protocol, targeted non-systematic keyword searches were conducted to identify CPGs for the use of oral magnesium for the indications listed on Swissmedic. These searches were conducted prior to consulting Swiss clinical experts, to obtain specific information on the prescribing of oral magnesium in clinical practice in Switzerland. The findings of these searches and expert advice from clinicians both formed the basis of the indications included/excluded in this HTA protocol. The rationale for the exclusion of any indication listed on Swissmedic, where oral magnesium is covered by mandatory health insurance, is provided below.

11.4.1 Known hypomagnesaemia and primary prevention

Treatment with oral magnesium in patients with known hypomagnesaemia does not fall within the remit of this HTA. In Swiss clinical practice, those with proven hypomagnesaemia (via laboratory evaluation) should receive supplementation, and can access oral magnesium to manage this condition, therefore this indication will not be a focus of this HTA.

Of particular interest to this HTA protocol are indications where patients without proven hypomagnesaemia receive oral magnesium as treatment to prevent relapse/recurrence of health

problems or to prevent complications related to other interventions that do not cause hypomagnesaemia.

Primary prevention with oral magnesium does not fall within the remit of this HTA as mandatory health insurance (OKP) does not routinely pay for preventative interventions, unless prespecified. Primary prevention aims to prevent a disorder before it occurs. Examples of primary prevention are immunisation or education about healthy habits such as exercising regularly. Thus, those with known hypomagnesaemia and its use in primary prevention are outside the scope of this HTA protocol.

11.4.2 Cardiac tachyarrhythmias

Intravenous (IV) magnesium may be used to prevent/treat cardiac tachyarrhythmias. The following information from CPGs has been identified to support the use of IV magnesium for cardiac tachyarrhythmias:

- European Society of Cardiology guidelines (2022) for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommends the use of IV magnesium with supplementation of potassium in patients with Torsades de Pointes.[86]
- American College of Cardiology/American Heart Association/Heart Rhythm Society guideline (2015) for the management of adult patients with supraventricular tachycardia mentions that IV magnesium may also be helpful in patients with normal magnesium levels with multifocal atrial tachycardia.[87]
- American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society guideline (2023) for the diagnosis and management of atrial fibrillation concludes that IV magnesium may be effective at rate-controlling rapid atrial fibrillation, and also used in combination with other antiarrhythmic drugs.[88]
- Some guidelines suggest the use of IV magnesium for the prevention of atrial fibrillation after cardiothoracic surgery.[89]

No supporting information from guidelines was identified for the use of oral magnesium for cardiac tachyarrhythmias, so information was sought from Swiss clinical experts to understand current practice in Switzerland.

The cardiologists consulted suggested that oral magnesium is not prescribed by cardiologists for cardiac tachyarrhythmias. However, both cardiologists (adult and paediatric) suggested that oral magnesium may be prescribed in outpatient care (i.e. general practice) for supraventricular premature contractions and premature ventricular contractions. Whether or not these types of contractions constitute a tachyarrhythmia appears to be a point of debate. Upon reference to International Classification of Diseases 11th Revision (ICD-11) classifications for these specific types of contractions, supraventricular premature contractions and premature ventricular

contractions fall outside of what would constitute a tachyarrhythmia and therefore are outside the scope of the listed Swissmedic indications.

In response to the clinician feedback received, and the lack of reference to oral magnesium in CPGs for tachyarrhythmias, Swissmedic indications and ICD-11 classifications, this indication was excluded from the HTA protocol.

11.4.3 Coronary heart disease

No information from published CPGs was identified on the use of oral magnesium in coronary heart disease management,[90] so information was sought from Swiss clinical experts to understand current practice in Switzerland.

Both cardiologists (adult and paediatric) suggested there is no indication for the use of oral magnesium in coronary heart disease and other medications would be used in Switzerland; therefore, this indication was excluded from the HTA protocol.

11.4.4 Impending late abortion or prodrome of early delivery

None of the identified guidelines from New South Wales (NSW) Health,[91] WHO[92] the National Institute for Health and Care Excellence (NICE),[93] Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG),[94] or joint guideline by SGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) and Oesterreichische Gesellschaft fur Gynakologie und Geburtshilfe (OEGGG)[95] recommended the use of oral magnesium for delaying impending premature delivery. However, a number of these guidelines recommend the use of IV magnesium sulphate for neuroprotection,[91,92,95] and it seems that it can be used for tocolysis/maintenance tocolysis, although other tocolytic agents have greater benefits and fewer side effects.[92,94] Whereas, the joint guideline by SGGG, DGGG and OEGGG (2022)[95] no longer recommend the use of IV magnesium sulphate for tocolysis due to lack of evidence-based proven tocolytic efficacy.

Information was sought from 2 Swiss clinical experts to understand current practice in Switzerland. The obstetrician and paediatrician consulted suggested there is no role for IV magnesium in impending late abortion or prodrome early delivery, and that other tocolytics would be used for this indication in Switzerland. However, the obstetrician suggested that oral magnesium is used in Switzerland to manage uterine cramping at any stage of pregnancy, even when there is no cervical shortening—despite the absence of official guidelines for this practice. The obstetrician stated that if uterine cramping without cervical changes is considered (by a clinician) as an early stage of 'impending late abortion or prodrome early delivery,' then its use aligns with the licensed indication. Uterine cramping can progress to contractions, with or without cervical shortening. The obstetrician stated that, 'if cervical shortening occurs, tocolytic medication is introduced (as per tocolysis guideline recommendations) alongside oral magnesium (although no guidelines recommend this practice). However, the distinction between symptom management (cramping relief) and prevention of preterm complications remains unclear. Despite the conflicting clinical expert advice,

given the lack of established clinical guidelines recommending the use of oral magnesium in treating uterine cramping with or without cervical shortening during pregnancy, this indication was excluded from the HTA protocol.

11.4.5 (Pre-) eclampsia

Magnesium may be used in cases of eclampsia (seizures) and pre-eclampsia as an anticonvulsant. However, this applies to IV magnesium sulphate. There is limited evidence to support the use of oral supplementation. The following information from clinical guidelines has been identified to support the use of IV magnesium for (pre-) eclampsia:

- The NICE guideline (2019) for hypertension in pregnancy diagnosis and management[96] indicates that IV magnesium sulphate can be used as an anticonvulsant for the treatment of eclampsia in pre-eclampsia. This guideline recommends against routinely prescribing oral magnesium to prevent pre-eclampsia.
- Guidelines from Queensland Health (2021) on hypertension and pregnancy[97] and guidelines from the German Society for Obstetrics and Gynecology (2024)[98] state that IV magnesium sulphate can be used as an anticonvulsant for the treatment of eclampsia in pre-eclampsia, but not as a general treatment for hypertension in pregnancy. Additionally, the Queensland Health guidance on hypertension and pregnancy[97] indicate that there is insufficient evidence to recommend the routine administration of oral magnesium supplements to prevent or treat hypertensive disorders during pregnancy.

No supporting information from guidelines was identified to support the use of oral magnesium for (pre-) eclampsia, so information was sought from Swiss clinical experts to understand current practice in Switzerland.

The obstetrician consulted, indicated that oral magnesium would only be prescribed to manage the bowel (i.e. for the laxative side effect) in women with (pre-) eclampsia, but not specifically to treat the (pre-) eclampsia itself. A paediatrician consulted, indicated that IV magnesium may be used but not oral magnesium. Thus, this indication was excluded from the HTA protocol.

11.4.6 Neuromuscular hyperexcitability or muscle twitches

No guidelines were found for the treatment of neuromuscular hyperexcitability. This is a syndrome rather than a condition. It may be observed in multiple rare diagnoses including cramp-fasciculation syndrome, Isaacs syndrome and Morvan syndrome.[99] Further information was sought from a Swiss clinical expert to understand current practice in Switzerland.

The Swiss neurologist confirmed that these conditions (i.e. Isaacs syndrome, Morvan syndrome, neuromyotonia) are incredibly rare, with low case numbers. Due to the clinical feedback received and an anticipated lack of available evidence, this indication was excluded from the HTA protocol.

Muscle twitches (e.g. fasciculations) are also a symptom as opposed to a condition. No CPGs were identified, so Swiss clinical experts were consulted. The Swiss neurologist stated that muscle twitches are typically unnoticeable and are rarely treated. Thus, this indication was excluded from the HTA protocol.

11.4.7 Restless legs syndrome

Of the CPGs identified for restless leg syndrome, none recommended oral magnesium to manage the condition. Three guidelines[100-102] state there is insufficient evidence to support its use; one guideline[103] makes no mention of magnesium at all. Information was sought from Swiss clinical experts to understand current practice in Switzerland.

The neurologist consulted suggested that oral magnesium is not used in clinical practice by neurologists and is not recommended in CPGs relevant to Swiss practice. (According to the neurologist, it is unknown whether it is prescribed in general practice but it is expected that GPs should know not to prescribe it for restless legs syndrome.) The paediatrician consulted, noted that oral magnesium may sometimes be used but it is not recommended and there is no clear clinical rationale for its use.

Based on the clinical feedback received and the lack of any reference to oral magnesium in CPGs for restless leg syndrome, this indication was excluded from the HTA protocol.

11.4.8 Tetanic syndrome

No guidelines were found for the treatment of tetany as it is a symptom rather than a condition. It usually occurs as a result of an electrolyte imbalance (e.g. hypomagnesaemia or hypocalcaemia), with guidelines focusing on treating the underlying electrolyte imbalance/deficiency not the symptom itself.[8,104] Information was sought from Swiss clinical experts to understand current practice in Switzerland.

The neurologist consulted, suggested that tetanic syndrome is an outdated term not used in current diagnoses: the indication is for the symptom of tetany. The neurologist suggested that the symptom is rarely seen, and oral magnesium would not be indicated regardless. The paediatrician consulted, suggested there is no clinical rationale for using oral magnesium for this indication. Thus, this indication was excluded from the HTA protocol.

11.5 NRSI potential confounding factors

Potential confounding factors were identified from the published literature including SRs, RCTs and NRSI via the exclusion criteria listed for participant enrolment. Any additions or items removed from this list prior to the assessment of ROBINS-I V2 will be listed as protocol amendments in the full HTA.

11.5.1 Calcium oxalate urolithiasis

1. *Age and gender:* Stone formation generally increases with age, with reduced magnesium absorption, and with higher levels of metabolic disorders more common in older adults that may reduce the effectiveness of magnesium supplements. Additionally, men are at a higher baseline risk for calcium oxalate urolithiasis and may benefit more from the inhibitory effects of magnesium.[105-107]

2. *Baseline urinary magnesium levels:* Higher urinary magnesium excretion levels protect against the formation of calcium oxalate urolithiasis by inhibiting crystallisation, while individuals with low excretion levels are more likely to benefit from supplementation to increase magnesium concentrations in urine.[36]

3. *Urinary oxalate, calcium and pH levels:* Increased urinary oxalate promotes the formation of calcium oxalate urolithiasis; however, magnesium can bind oxalate in the gastrointestinal tract, reducing its urinary excretion and stone risk. This effect is more pronounced in individuals with high oxalate levels, while those with normal excretion may see less benefit from magnesium supplementation. Magnesium may also help alkalinise acidic urine, lowering calcium oxalate supersaturation and reducing stone risk, although its effect is limited in patients who already have alkaline urine. Additionally, magnesium competes with calcium for oxalate binding, mitigating stone formation in individuals with hypercalciuria, whereas the impact of magnesium supplementation may be less significant in those with normal urinary calcium levels.[106,107]

4. *Diet and lifestyle:* Magnesium binds to dietary oxalate, reducing absorption and urinary excretion, making magnesium supplementation more effective in those consuming oxalate-rich foods.[39,108] Other dietary factors such as high dietary calcium, high dietary sodium, high dietary (animal) protein, and low dietary citrate may also contribute to calcium oxalate urolithiasis and the overall effectiveness of magnesium supplementation.[39]

5. *Hydration status:* Dehydration increases urinary supersaturation of stone-forming salts, therefore those with inadequate hydration are more likely to experience improvements from magnesium supplementation than those who are adequately hydrated.[39]

6. *Underlying health issues:* There is the potential for underlying health issues to alter the effectiveness of magnesium supplementation. These health issues may include primary hyperoxaluria, hypercalciuria, hyperuricosuria, hyperkalaemia, hyperparathyroidism, obstructive uropathy, chronic urosepsis, renal insufficiencies/failure, renal tubular acidosis, diabetes and disease/malabsorption conditions (e.g. Crohn's disease, ulcerative colitis, short bowel syndrome).[105,107]

7. *Medication use and medical intervention:* Certain medications and dietary supplements may increase magnesium losses, impair absorption or increase the likelihood of calcium oxalate urolithiasis. These supplements/medications include calcium, vitamin C, vitamin D, antibiotics, loop diuretics, glucocorticoids, carbonic anhydrase inhibitors and laxatives (when abused).[109,110] Other medications or dietary supplements that have been prescribed specifically for calcium oxalate urolithiasis are also likely to confound the results (e.g. potassium/sodium citrate salts, thiazide and allopurinol).[39,105,110] The application of medical interventions immediately prior to or during the study period must also be investigated (e.g. double J catheter insertion, shock wave lithotripsy, cystoscopy, ureteroscopy or percutaneous nephrolithotomy).

8. *Duration and severity of disease:* Patients with recurrent stones may experience more benefits from magnesium supplementation than those with minimal stone history.[105] Additionally, other disease features of calcium oxalate urolithiasis may also impact the effectiveness of magnesium supplementation, including presence of residual stones, size and location of stones, and urinary tract infection.[106,107]

11.5.2 Muscle cramps

1. *Baseline magnesium levels:* Individuals with low magnesium levels are more likely to benefit from magnesium supplementation. Individuals with normal levels may not experience improvements as their cramps are caused by other underlying issues. Individuals already taking magnesium supplements prior to enrolment may confound results if proper washout is not conducted.[111]

2. *Age:* Older adults with a decline in absorption and increased excretion of magnesium may respond more favourably to magnesium supplementation than younger adults.[65,112]

3. *Underlying health issues:* The potential exists for underlying health issues to alter the effectiveness of magnesium supplementation (both positively and negatively). These health issues may include impaired renal function, diabetes, neuropathy, oedema, major neurological disease (e.g. amyotrophic lateral sclerosis, multiple sclerosis, paraplegia or quadriplegia), hyper- or hypothyroidism, and those receiving haemodialysis.[4,63,111,113]

4. *Hydration status or electrolyte imbalance:* Dehydration or imbalances in sodium, potassium and calcium may exacerbate cramps.[112]

5. *Diet and lifestyle:* Poor dietary intake of magnesium-rich foods may increase the likelihood of cramps due to low dietary magnesium intake. Alcoholism or alcohol intake depletes magnesium levels and may make supplements more effective at reducing cramps.[4,112]
6. *Activity level:* Individuals engaging in high levels of physical activity may response better to magnesium supplementation due to increased muscle usage and losses through sweat. Those with low levels of physical activity or sedentary lifestyle may not respond as well to magnesium supplementation due to poorer circulation.[114]
7. *Medication use:* Certain medications may increase magnesium losses, impair absorption, or increase the likelihood of cramps. These medications include diuretics, statins and proton-pump inhibitors.[4,63] Other medications or dietary supplements prescribed specifically for cramps are also likely to confound the results (e.g. carisoprodol, diltiazem, gabapentin, verapamil, vitamin B12, vitamin D, vitamin E, vitamin B6).[4,63,111,113,115]
8. *Pregnancy:* Individuals who are pregnant are more likely to experience cramps due to magnesium depletion and may experience increased benefits from magnesium supplementation.[4,63,111,113]