Health Technology Assessment (HTA)

HTA Protocol

Title	Calcitonin gene-related peptide antagonists for the prevention of migraine
Author/Affiliation	Konstance Nicolopoulos, Royal Australasian College of Surgeons Ross McLeod, Royal Australasian College of Surgeons Joanna Duncan, Royal Australasian College of Surgeons
Technology	Erenumab (Aimovig®) Fremanezumab (Ajovy®) Galcanezumab (Emgality®) Eptinezumab (Vyepti®) Pharmaceutical
Date	8 July 2022

Executive Summary

This protocol outlines the methodological approach for a health technology assessment (HTA) report evaluating the effectiveness, safety, costs, cost-effectiveness and budget impact of calcitonin gene-related peptide (CGRP) antagonists compared to standard of care medications in patients who suffer from episodic and/or chronic migraine. The financial consequences of a positive reimbursement decision, provided the drugs are efficacious and safe, is of particular interest.

There are 4 CGRP antagonists approved by the Swiss Agency for Therapeutic Products (Swissmedic). Erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) are provisionally listed on the Spezialitätenliste until February 2024, February 2024, April 2024 and April 2024, respectively.

For the evaluation of clinical outcomes, a systematic literature search of biomedical databases (PubMed, Embase, Cochrane Library) will be conducted. Best available evidence will be selected, analysed and critically appraised for risk of bias using design-appropriate tools, and meta-analyses will be performed to synthesise outcomes where appropriate.

For the evaluation of economic outcomes, a systematic review and a critical analysis of identified economic studies will be used to determine the most appropriate method (e.g. cost-utility analysis using a hybrid decision and Markov model). The analysis will utilise up-to-date Swiss-specific cost inputs and clinical inputs that are most applicable to the Swiss context. Results will be outlined for a base case and cost-effectiveness acceptability curves will be presented as part of sensitivity analyses, along with results based on differing time horizon, discount rates, medicine prices, unit costs, clinical inputs and utility estimates. A budget impact analysis will also be conducted. The analysis will project costs (Swiss francs [CHF]) to the payer over the next 5 years using selected current and possible future policy and pricing scenarios.

Table of contents

Tables

Abbreviations

CI	Confidence interval
CEA	Cost-effectiveness analysis
CGRP	Calcitonin gene-related peptide
CHF	Swiss francs
CUA	Cost-utility analysis
DRG	Diagnosis-related group
EUR	euro
EQ-5D	EuroQol 5-dimension questionnaire
FMH	Foederatio Medicorum Helveticorum/Swiss Medical Association
FOPH	Federal Office of Public Health/Bundesamt für Gesundheit (BAG)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEpro GDT	GRADEpro Guideline Development Tool
HIT-6	Headache Impact Test
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
IHE	Institute of Health Economics
IHS	International Headache Society
INAHTA	International Network of Agencies for Health Technology Assessment
IV	Intravenous
MCID	Minimum clinical important difference
MD	Mean difference
MHDs	Monthly headache days
MMDs	Monthly migraine days
MSQ	Migraine-Specific Quality of Life questionnaire
NHS EED	National Health Service Economic Evaluation Database
OKP	Swiss mandatory health insurance (obligatorische Krankenpflegeversicherung)
PICO	Population, intervention, comparator, outcome
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised control trial
RoB 2.0	Cochrane risk-of-bias tool, version 2
RR	Risk ratio
SD	Standard deviation

SE	Standard error
SF-36	36-Item Short Form Health Survey
SKG	Swiss Headache Society (Schweizerische Kopfwehgesellschaft)
SMD	Standardised mean difference
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objectives of the HTA Protocol are to formulate the research question; define the population, intervention, comparator, outcomes (PICO); and describe the methodology to conduct a systematic literature search and extract, analyse and synthesise the data in the HTA report on the topic. For this HTA report, key questions will be formulated addressing the HTA domains efficacy/effectiveness/safety and costs/budget impact/cost-effectiveness.

1 Policy question

Each HTA topic entails policy and research questions. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, may address a new developing technology or an older technology for which reimbursement has been questioned. The topic of this HTA report entails the evaluation of the migraine prevention class of drugs targeting the calcitonin gene-related peptide (CGRP) and its receptor, including the monoclonal antibodies erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®).

Of particular interest are the financial consequences of a positive reimbursement decision, provided the drugs are efficacious and safe.

There are 4 CGRP antagonists approved by the Swiss Agency for Therapeutic Products (Swissmedic).[1] Erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) are provisionally listed on the Spezialitätenliste[2] until February 2024, February 2024, April 2024 and April 2024, respectively.

2 Research question

To answer a policy question, a research question has to be defined and answered first. The ***research question*** is an answerable inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow. This HTA report addresses the following research question:

For the prevention of migraine, are CGRP antagonists clinically efficacious, safe and cost-effective compared to the current standard of care?

3 Medical background

3.1 Medical context, disease description and main symptoms

Migraine is a common neurological disease. Considered to be one of the most debilitating conditions, it affects approximately 15% of the adult population.[3,4] Migraine headaches are often characterised by moderate to severe attacks of unilateral, throbbing head pain, often accompanied by visual, sensory, motor and speech/language disturbances, lasting 4–72 hours.[5]

Migraines are defined and classified using the International Classification of Headache Disorders (ICHD) (3rd edition).[6] According to ICHD diagnostic criteria, migraine is categorised as: (1) migraine without aura; (2) migraine with aura.[6]

Migraine without aura is defined as a recurring headache disorder, with attacks lasting 4–72 hours when untreated or treated unsuccessfully.[6] Migraine without aura is characterised by at least 2 of the following headache symptoms: located unilaterally, throbbing sensation, moderate to severe pain intensity, aggravated by physical activity or leading to avoidance of such activity, as well as one of the following: nausea and/or vomiting or photophobia and/or phonophobia.[6]

Migraine with aura can further be broken down into 4 subtypes: (1) migraine with typical aura; (2) migraine with brainstem aura; (3) hemiplegic migraine; (4) retinal migraine.[6] Migraine with aura is defined as a recurring headache disorder, with aura attacks usually lasting ≤60 minutes and then followed by common headache and migraine symptoms.[6] Migraine with aura is characterised by at least 2 of the following reversible aura symptoms: visual, sensory, speech/language, motor, brainstem and/or retinal disturbances, along with 3 of the following aura characteristics: at least one aura symptom that spreads slowly over ≥5 minutes, 2 or more aura symptoms occurring at the same time, each aura symptom lasting 5–60 minutes, at least one aura symptom being located unilaterally and/or developing positive phenomena (e.g. false visual images), along with the aura being followed by common headache and migraine symptoms within 60 minutes of onset.[6]

Per the ICHD diagnostic criteria, **chronic migraine** is characterised by 15 or more headache days per month, for 3 months or more, with at least 8 headache days per month having features of a migraine,[6] whereas **episodic migraine** is characterised by fewer than 15 headache days per month.[6] As per expert advice, these definitions are consistent with those used in clinical practice in Switzerland.[7]

3.2 Burden of disease

In 2016, the Global Burden of Disease Study[4] estimated that 1.04 billion people worldwide experienced migraine, contributing to 45.1 million years of life lived with disability. Furthermore, it was estimated that migraine effects approximately 1.6 million people in Switzerland, resulting in around 70,000 years of life lived with disability in 2016.[4] In a cohort study of 4,547 people, representative of the canton of Zurich, the cumulative 30-year prevalence (1978–2008) of migraine with aura was estimated to be 3% (2.1% in males; 3.9% in females), whereas the cumulative 30-year prevalence of migraine without aura was 36% (20.7% in males; 50.7% in females).[8] Migraine is 2 to 3 times more prevalent in females than males, with females suffering from both migraine with aura and migraine without aura at a higher rate.[8,9]

In Europe, it has been estimated that the total annual cost of migraine is around Euro (EUR)111 billion, with a mean per-person annual cost of migraine of EUR1,222 among adults aged 18–65 years. This

estimate includes direct (medicines, outpatient healthcare, hospitalization) and indirect (reduced labour productivity) costs.[10] The review of Stovner and Andrée[11] found that approximately 72–98% of migraine-related costs can be attributed indirectly to work productivity losses, including work absences or reduced output when working with a migraine, while around 30% are associated with direct costs such as appointments, diagnostic tests, treatments and hospital stays.

3.3 Treatment pathways

There is no cure for migraine; however, it can be managed with non-pharmacological treatments, acute therapies or prophylactic treatments:

- Non-pharmacological migraine treatments are recommended by guidelines as a first-line therapy and are commonly used in combination with pharmacological agents to treat migraine; these typically involve lifestyle changes, mindfulness activities and supplementation to reduce symptoms.[7,12] They include aerobic exercise, behavioural and psychological therapies, stress management and relaxation techniques, acupuncture and massage, and supplementation (e.g. magnesium, riboflavin, coenzyme Q10).[13]
- Acute therapies are used to alleviate the symptoms associated with migraine at the time of attack in order to limit disability and reduce the pain associated with migraine symptoms.[9,14] Acute therapies include analgesics (e.g. paracetamol, aspirin, nonsteroidal anti-inflammatory drugs), antiemetics (e.g. metoclopramide, domperidone) and triptans (e.g. rizatriptan, sumatriptan, zolmitriptan).[14] Alternatively, prophylactic treatments aim to prevent and reduce the frequency, severity and duration of expected migraine attacks in those with a history of migraine.[9,14]
- Prophylactic therapies include beta blockers (e.g. propranolol, metoprolol), calcium antagonists (e.g. flunarizine), anticonvulsants (e.g. topiramate), antidepressants (e.g. amitriptyline) and CGRP antagonists (e.g. erenumab, fremanezumab, galcanezumab and eptinezumab).[13,14] These prophylactic treatments, with the exception of CGRP antagonists, are considered to be the standard of care for migraine prevention in Switzerland.[12,15-17]

Non-pharmacological migraine treatments are recommended by clinicians prior to the initiation of pharmacological treatments;[7] however, where these treatments are ineffective at limiting migraine on their own, pharmacological treatments are also incorporated into the management of symptoms in these patients.[7] Through consultation with a medical professional, the decision of which drug to choose is based on: (1) level of evidence; (2) migraine subtype, frequency and disability; (3) medication side effects, comorbidities and concomitant medication; (4) patient characteristics and preference; (5) response to previous treatments; (6) contraindications/allergies; (7) cost and insurance coverage.[7,18]

Typically, the choice of treatment will begin with a titration phase of the most tolerable/safest treatment, and then progressively initiate alternative treatments with a higher number of possible side effects if the last treatment was found to be intolerable or ineffective after 8–12 weeks (Example treatment pathway: riboflavin and/or coenzyme Q10 > magnesium > beta blocker > anticonvulsant).[7,18] In cases of failure of more than 2 standard of care medications (i.e. beta blockers, calcium antagonists, anticonvulsants or antidepressants), only then are CGRP antagonists considered as a treatment option.[7] In Switzerland, the prescription of CGRP antagonists and follow-up may only be carried out by a Foederatio Medicorum Helveticorum (FMH)/Swiss Medical Association-certified specialist in neurology.

Advancement in migraine research has resulted in the development of newer treatments for the management of migraine.[19,20] These treatments include the CGRP antagonists—erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®)—which are the only disease-specific preventative treatments for migraine.[19,20] It is hypothesised that the CGRP receptor may be involved via its role in the vasodilation of meningeal and cerebral blood vessels and/or its role in activating trigeminal sensory nerve fibres which results in a pain response and subsequent inflammation.[21,22] Additionally, it has been demonstrated that CGRP is released and detected at higher levels during migraine attacks, with CGRP levels normalising after treatment, therefore CGRP may play a role in inducing migraine attacks.[21]

4 Technology description

Four monoclonal antibodies that target CGRP or its receptors—erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®)—have been approved by the Swiss Agency for Therapeutic Products (Swissmedic)[1,15] for migraine prophylaxis since July 2018, March 2019, December 2019 and May 2022, respectively, and have been provisionally listed on the Spezialitätenliste[2] until February 2024, February 2024, April 2024, and April 2024, respectively. These treatments are currently reimbursed by Swiss mandatory health insurance (obligatorische Krankenpflegeversicherung [OKP]) for a specific patient population; this is summarised in ***Appendix A***.

Briefly, erenumab (AMG334) is a human monoclonal antibody that binds to the CGRP receptor and blocks its function.[20] Fremanezumab (TEV48125) is a fully humanised monoclonal antibody that selectively targets CGRP isoforms, preventing CGRP from binding to its receptors.[20] Galcanezumab (LY2951742) is a humanised monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor.[20] Eptinezumab (Vyepti®) is a humanised monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor.[23] ***Table 1*** provides additional details on the characteristics of each of these treatments.

The selection of an appropriate CGRP antagonist (i.e. erenumab, fremanezumab, galcanezumab or eptinezumab) is dependent on a number of factors, including:

- patient preference (i.e. administered monthly [erenumab, fremanezumab, galcanezumab] vs quarterly [fremanezumab at a higher dose, or eptinezumab])
- contraindications
- the overall effectiveness of each treatment on the biological target at an individual level (i.e. treatment that targets the CGRP receptor [erenumab] vs the ligand [fremanezumab, galcanezumab, eptinezumab]).[7,24]

As per © COGE GmbH Tarifpool © SASIS AG sales data from 2020, erenumab is the most utilised CGRP antagonist in Switzerland—with the largest number of packs sold (84.4%)—followed by galcanezumab (13.9%), then fremanezumab (1.7%); similar usage trends have been observed for 2021 (data not yet complete).[25]

4.1 Alternative technologies

4.1.1 Beta blockers

Beta blockers are also commonly prescribed for the prophylactic treatment of migraine. As per the Swiss Headache Society/Schweizerische Kopfwehgesellschaft (SKG), 2 beta blockers are approved for use in Switzerland—propranolol and metoprolol.[15] Propranolol is available in 4 formulations, while metoprolol is available in 8 formulations (see ***Table 1***). The exact mechanism of action of beta blockers on the prevention of migraine is still unclear; however, it is thought that they assist in stabilising cranial blood vessels by preventing them from over-dilating, as this over-dilation is believed to be a trigger of migraines.[26] Propranolol is administered orally via a tablet at a 10–320 mg dosage per day, with the recommended dosage for migraine prophylaxis being 80–160 mg per day.[1] Metoprolol is administered orally via a tablet at a 25–200 mg dosage per day, with the recommended dosage for migraine prophylaxis being 100–200 mg per day.[1]

4.1.2 Calcium antagonists

For the prevention of migraine, a single calcium antagonist—flunarizine (Sibelium®, Janssen-Cilag AG)—is approved for use in Switzerland.[15] Flunarizine acts as a calcium channel blocker, which is hypothesised to counteract the narrowing of cerebral blood vessels, which may ultimately prevent migraine.[27] Flunarizine is administered orally via a tablet at a 5–10 mg dosage per day, with the recommend dosage for migraine prophylaxis being 5 mg per day.[1]

4.1.3 Anticonvulsants

Certain anticonvulsants may also be prescribed for the prophylactic treatment of migraine in adults. Topiramate is currently the only anticonvulsant approved for use in Switzerland.[15] This drug is available in 3 formulations (see ***Table 1***). The exact mechanism of action of topiramate is unclear; however, it is thought that it prevents the action of voltage-gated sodium channels, leading to the prevention of migraine.[28] Topiramate is administered orally via a tablet at a 25–400 mg dosage per day; however, the recommended dose for migraine prophylaxis is 100 mg per day.[1,28]

4.1.4 Antidepressants

Antidepressants are another class of medication that can be prescribed for the prophylactic treatment of migraine in adults. In Switzerland, amitriptyline (Saroten®, Lundbeck [Schweiz] AG) is currently approved for use.[15] Amitriptyline is a tricyclic antidepressant that inhibits serotonin and norepinephrine uptake.[29] Amitriptyline is administered orally via a tablet. It can be administered at a 10–150 mg dosage per day, although for the prophylaxis of migraine it is typically administered at doses lower in the range (e.g. 25–75 mg per day).[1,29]

Refer to ***Table 1*** for additional details of the described alternative technologies.

Table 1 Prophylactic treatments for the prevention of migraine

***Drug:* brand name/ (manufacturer)**	**Dosage, administration and pharmaceutical form**	**Indications**	**Half life**	**Metabolism**	**Contraindications**
CGRP antagonists					
Erenumab: Aimovig® (Novartis Pharma Schweiz AG)	70 mg in 1 ml solution (70 mg/ml) monthly 140 mg in 1 ml solution (140 mg/ml) monthly † (available in a single pre-filled pen) Subcutaneous injection (pre-filled pen)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	28 days	Degraded into peptides and amino acids by enzymatic proteolysis[30]	Hypersensitivity to active ingredient or any other ingredient in solution; latex allergy, constipation or hypertension[31]
Fremanezumab: Ajovy® (Teva Pharma AG)	225 mg in 1.5 ml solution (150 mg/ml) monthly 675 mg quarterly (3 pre-filled pens) Subcutaneous injection (pre-filled pen/syringe)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	30 days	Degraded into peptides and amino acids by enzymatic proteolysis[30]	Hypersensitivity to active ingredient or any other ingredient in solution
Galcanezumab: Emgality® (Eli Lilly [Suisse] SA)	120 mg/ml once monthly (starting dose of 240 mg/ml, 2 pre-filled pens) Subcutaneous injection (pre-filled pen)	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	27 days	Degraded into peptides and amino acids by enzymatic proteolysis[30]	Hypersensitivity to active ingredient or any other ingredient in solution
Eptinezumab: Vyepti® (Lundbeck [Schweiz] AG)	100 mg in 1 ml solution (100 mg/ml) quarterly 300 mg in 1 ml solution (300 mg/ml) quarterly Intravenous (IV) infusion	Prophylactic treatment for migraine in adults if indicated (see ***Appendix A***)	27 days	Degraded into peptides and amino acids by enzymatic proteolysis[30]	Hypersensitivity to active ingredient or any other ingredient in solution
Beta blockers					
Propranolol: Propranolol Helvepharm (Helvepharm AG)* Propranolol retard Helvepharm (Helvepharm AG)# Propranolol Zentiva (Helvepharm AG)* Propranolol retard Zentiva (Helvepharm AG)#	Recommended dose for migraine: 80–160 mg daily Dosage range: 10–320 mg daily Oral administration * Available in 10, 40 and 80 mg tablets # Available in 160 mg capsules * Available in 10, 40 and 80 mg tablets # Available in 160 mg capsules	Hypertension; angina; anxiety; essential tremor; pheochromocytoma; long-term prophylaxis after myocardial infarction; portal hypertension; oesophageal varices; prophylactic treatment for migraine in adults	3–6 hours	Hepatic metabolism, into metabolites[32]	Hypersensitivity to active ingredient or any other ingredient in tablet; bronchial asthma; bronchospasm; bradycardia; hypotension; heart failure; 2nd/3rd degree AV blockage; cardiogenic shock; Prinzmetal's angina; peripheral circulatory disorders; sick sinus syndrome; pheochromocytoma; metabolic acidosis; hyperglycaemia; long-term fasting
Metoprolol: Beloc Zok 25/50/100/200 (Recordati AG)*	Recommended dose for migraine: 100–200 mg daily Dosage range: 25–200 mg daily Oral administration *Available in 25, 50, 100 and 200 mg tablets	Hypertension; angina; chronic heart failure; cardiac arrhythmias; cardiovascular disorders with palpitations; prophylactic treatment for migraine in adults	3.5 hours	Oxidatively degraded in the liver, into 3 metabolites[33]	Hypersensitivity to active ingredient or any other ingredient in tablet; other beta blockers; bronchial asthma; bronchospasm; bradycardia; hypotension; heart failure; 2nd/3rd degree AV blockage; cardiogenic shock; peripheral circulatory disorders;

Drug: brand name/ (manufacturer)	Dosage, administration and pharmaceutical form	Indications	Half life	Metabolism	Contraindications
Logimax (Recordati AG)# Lopresor 100/retard (Daiichi Sankyo [Schweiz] AG)§ Meto Zerok (Sandoz Pharmaceuticals AG)* Metoprolol Axapharm (Axapharm AG)* Metoprolol Helvepharm (Helvepharm AG)* Metoprolol Mepha (Mepha Pharma AG)* Metropolol Spirig HC (Spirig HealthCare AG)*	# Available in 5/50 and 10/100 mg tablets (also containing 5 or 10 mg of felodipine) § Available in 100 and 200 mg tablets *Available in 25, 50, 100 and 200 mg tablets *Available in 25, 50, 100 and 200 mg tablets *Available in 25, 50, 100 and 200 mg tablets *Available in 25, 50, 100 and 200 mg tablets *Available in 25, 50, 100 and 200 mg tablets				sick sinus syndrome; acute myocardial infarction; pheochromocytoma
Calcium antagonists					
Flunarizine: Sibelium® (Janssen-Cilag AG)	Recommended dose for migraine: 5 mg daily (single administration) Dosage range: 5–10 mg daily Oral administration Available in 5 mg tablets	Prophylactic treatment for migraine in adults; vestibular balance disorders	5–15 hours	Hepatic metabolism into 15 metabolites[34]	Hypersensitivity to active ingredient or any other ingredient in tablet; depression; extrapyramidal symptoms or Parkinson's disease
Anticonvulsants					
Topiramate: Topamax (Janssen-Cilag AG) Topiramat Sandoz (Sandoz Pharmaceuticals AG) Topiramat Spirig HC (Spirig HealthCare AG)	Recommended dose for migraine: 100 mg daily (50 mg divided into 2 individual administrations) Dosage range: 25–400 mg daily Oral administration Available in 25, 50, 100 and 200 mg tablets ‡	Epilepsy; prophylactic treatment for migraine in adults	21 hours	Metabolites not known to be active Characterised by reactions of glucuronidation, hydroxylation and hydrolysis Approximately 70% eliminated unchanged in the urine[28]	Hypersensitivity to active ingredient or any other ingredient in tablet; pregnancy and breastfeeding; women of childbearing age who do not use a safe contraceptive method[35]
Antidepressants					
Amitriptyline: Amitriptyline Saroten® (Lundbeck [Schweiz] AG)	Recommended dose for migraine: 25–75 mg daily Dosage range: 10–150 mg daily Oral administration Available as 10 and 25 mg tablets	Depressive disorders; neuropathic pain, prophylactic treatment of chronic tension headaches or migraine in adults	25 hours	Metabolised by demethylation and hydroxylation, followed by glucuronidation[36]	Hypersensitivity to active ingredient or any other ingredient in tablet; recent heart attack; any degree of heart valve blockage, arrhythmia or irregularities; simultaneous use with monoamine oxidase inhibitors

Abbreviations

AV = atrioventricular, **CGRP** = calcitonin gene-related peptide, **IV** = intravenous.

Notes

† In patients who do not experience sufficient effects from 70 mg/ml of erenumab (Aimovig®), dosage may be increased to 140 mg/ml of erenumab (Aimovig®), as long as sufficient effects can be demonstrated.

‡ Topamax (Janssen-Cilag AG) also available in 15 and 50 mg capsules.

Source

Swissmedic 2021[1], unless otherwise referenced in table

5 PICO

Table 2 PICO criteria

Population(s)	1. Patients who suffer from episodic migraine (i.e. characterised by less than 15 headache days per month)[6] **Subgroup 1:** Patients who suffer from episodic migraine (i.e. with migraine attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline) 2. Patients who suffer from chronic migraine (i.e. characterised by 15 or more headache days per month, for 3 months or more, with at least 8 migraine days per month)[6] **Subgroup 2:** Patients who suffer from chronic migraine (i.e. with migraine attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline) *Exclusion: Paediatric patients (<18 years)*
Intervention(s)	• Erenumab (Aimovig®)—70 or 140 mg once monthly • Fremanezumab (Ajovy®)—225 mg once monthly or 675 mg quarterly • Galcanezumab (Emgality®)—120 mg once monthly (starting dose of 240 mg) • Eptinezumab (Vyepti®)—100 mg or 300 mg quarterly

Comparator(s)	• Placebo
	• Standard of care for migraine prevention
	  ○ Beta blockers: propranolol, metoprolol
	  ○ Calcium antagonist: flunarizine
	  ○ Anticonvulsants: topiramate
	  ○ Antidepressants: amitriptyline
	• Other CGRP antagonists (i.e. comparing each of the interventions to each other)

Outcome(s)	**Clinical outcomes:** • Monthly migraine days (MMDs) and monthly headache days (MHDs) • Health-related and migraine-specific quality of life (e.g. HIT-6, MSQ, MIDAS, TPB, EQ-5D, SF-36) • Migraine/headache pain intensity (e.g. VAS, NRS) • Number of days per month with a migraine that needs to be treated with acute pain relievers (i.e. MMDs with acute medication use) • Response rate (defined as a reduction of the average number of days with migraines of at least 50% after 6 months of treatment compared to prior to the treatment beginning) • Treatment adherence • Mortality • Treatment-related adverse events (AEs) • Serious adverse events (SAEs) • Adverse events leading to discontinuation • Adverse events upon discontinuation of CGRP antagonists (e.g. rebound effect) **Health-economic outcomes:** • Costs, utilities, ICER, budget impact

Abbreviations
AEs = adverse events, **CGRP** = calcitonin gene-related peptide, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test, **ICER** = incremental cost-effectiveness ratio, **MHDs** = monthly headache days, **MIDAS** = Migraine Disability Assessment Scale, **MMDs** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NRS** = numerical rating scale, **SAEs** = serious adverse events, **SF-36** = 36-Item Short Form Health Survey, **TPB** = total pain burden, **VAS** = visual analogue scale.
Source
IHS 2018[6]

5.1 Population

There are 2 key populations of interest: patients who suffer from chronic migraine and patients who suffer from episodic migraines. As aforementioned, chronic migraine is characterised by 15 or more headache days per month, for 3 months or more, with at least 8 headache days per month having features of a migraine,[6] whereas episodic migraine is characterised by fewer than 15 headache days per month.[6] Additionally, 2 subgroups will also be included to reflect the Swiss context in which CGRP antagonists are used: (i) patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month), and (ii) patients who suffer from episodic migraines (i.e. with attacks that last at least 4 hours on at least 8 days per month) for a duration of at least one year (see ***Appendix A***, Item 3). Furthermore, prior to starting CGRP antagonist treatment, these subgroups must have trialled and failed to respond adequately to at least 2 other migraine prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or antidepressants) (see ***Appendix A***, Item 4).

5.2 Intervention

The following CGRP antagonists approved for use in Switzerland for a specific patient population (see ***Appendix A***) will be included: 70 or 140 mg erenumab (Aimovig®) once monthly, 225 mg once monthly or 675 mg quarterly of fremanezumab (Ajovy®), and galcanezumab (Emgality®) at a starting dose of 240 mg, then 120 mg per month thereafter—all administered via subcutaneous injection through a pre-filled pen/syringe. Finally, 100 or 300 mg eptinezumab (Vyepti®) quarterly—administered via intravenous (IV) infusion—will also be included.

5.3 Comparator

The comparators of interest include medications that are considered the standard of care for migraine prevention, each intervention (i.e. CGRP antagonists) to each other, and placebo. Standard of care medications for migraine prevention that are approved for use in Switzerland include beta blockers (i.e. propranolol and metoprolol), calcium antagonists (i.e. flunarizine), anticonvulsants (i.e. topiramate) and antidepressants (i.e. amitriptyline). All standard of care drugs are oral formulations taken on a daily basis.

5.4 Outcome

Relevant clinical outcomes include monthly migraine days (MMDs) and monthly headache days (MHDs), health-related and migraine-specific quality of life, migraine/headache pain intensity, number of days per month with a migraine that needs to be treated with acute pain relievers, response rate (defined as a reduction of the average number of days with migraines of at least 50% after 6 months of treatment

compared to prior to the treatment beginning), treatment adherence, mortality, treatment-related adverse events, serious adverse events, adverse events leading to discontinuation and adverse events upon discontinuation of CGRP antagonists (e.g. rebound effect). Health-economic outcomes are described in ***Section 7.5.1.4.***

The populations, interventions, comparators and outcomes in the PICO criteria (***Table 2***) follow the International Headache Society (IHS) position statement for the development of HTAs for the acute and preventative treatment of migraine.[17]

6 HTA key questions

For the evaluation of the technology, the following key questions covering the central HTA domains are addressed:

1. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from episodic migraine?
    a. Subgroup 1: Are CGRP antagonists for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
2. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from chronic migraine?
    a. Subgroup 2: Are CGRP antagonists for migraine prophylaxis effective/efficacious compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from chronic

migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

3. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from episodic migraine?
    a. Subgroup 1: Are CGRP antagonists for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
4. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from chronic migraine?
    a. Subgroup 2: Are CGRP antagonists for migraine prophylaxis safe compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]), other CGRP antagonists and placebo in patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
5. What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine?

a. Subgroup 1: What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

6. What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine?
    a. Subgroup 2: What are the costs associated with CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
7. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine?
    a. Subgroup 1: Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least

2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

8. Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine?
    a. Subgroup 2: Are CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis cost-effective compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
9. What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine?
    a. Subgroup 1: What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?
10. What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine?

a. Subgroup 2: What is the budget impact of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], eptinezumab [Vyepti®]) for migraine prophylaxis compared to the current standard of care (beta blockers [propranolol, metoprolol], calcium antagonists [flunarizine], anticonvulsants [topiramate], antidepressants [amitriptyline]) and other CGRP antagonists in patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline)?

6.1 Additional question(s)

11. In patients who suffer from episodic migraine, are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®), and eptinezumab (Vyepti®) CGRP antagonist effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], and eptinezumab [Vyepti®])?
    a. Subgroup 1: In patients who suffer from episodic migraine (i.e. with attacks that last at least 4 hours on at least 8 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline), are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®), and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], and eptinezumab [Vyepti®])?
12. In patients who suffer from chronic migraine, are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®), and eptinezumab (Vyepti®) CGRP antagonist effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], and eptinezumab [Vyepti®])?
    a. Subgroup 2: In patients who suffer from chronic migraine (i.e. with attacks that last at least 4 hours on at least 15 days per month) for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline), are erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab

(Emgality®), and eptinezumab (Vyepti®) effective/efficacious when used in patients who previously experienced inadequate treatment effects using a different CGRP antagonist (i.e. erenumab [Aimovig®], fremanezumab [Ajovy®], galcanezumab [Emgality®], and eptinezumab [Vyepti®])?

7 Methodology

7.1 Databases and search strategy

A systematic literature search will be conducted in 3 biomedical databases (PubMed, Embase, Cochrane Library). Key search terms related to the population and intervention will be combined and run through these databases. No search filters will be placed on the searches; however a date limit of 10 years will be placed on RCTs, and a date limit of 5 years will be placed on non-RCTs. Economic searches will include the same biomedical databases as the clinical search, plus EconLit, the National Health Service Economic Evaluation Database (NHS EED) and the cost-effectiveness analysis (CEA) Registry hosted by Tufts Medical Centre. The search strategy for PubMed is presented in ***Table 4***, ***Appendix B***, which will be adapted to the additional biomedical databases accordingly.

7.2 Other sources

Searches will be conducted in ClinicalTrals.gov and the EU Clinical Trials Registry to identify ongoing clinical trials related to CGRP antagonists for the prevention of migraine. Websites of HTA agencies that are members of the International Network of Agencies for Health Technology Assessment (INAHTA) will be searched to identify relevant HTA reports that include CEA (***Table 5***, ***Appendix C***).

7.3 Study selection

Results from the literature searches will be imported into Rayyan (Rayyan Systems Inc., United States).[37] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts.[37] The search results will be screened by title and abstract against the predetermined inclusion and exclusion criteria (***Table 6***, ***Appendix D***) by 2 reviewers. All articles deemed potentially relevant will then be reviewed in full text by each reviewer independently. Conflicts between reviewers on study inclusion will be settled via consensus at each stage of study selection. If consensus cannot be reached, a third reviewer will decide whether to include or exclude the citation.

Study selection will be limited to English, French, German and Italian language studies. French, German and Italian are three of the four official languages of Switzerland. The fourth language of Romansh will not be included because of the limited number of publications available.[38,39]

7.4 Study design

Studies will be prioritised for inclusion by study design using a hierarchical selection process. For each intervention, randomised control trials (RCTs) that meet the predetermined inclusion and exclusion criteria (***Table 6***, ***Appendix D***) will be included to assess the clinical effectiveness and safety of CGRP antagonists for the prevention of migraine. If no RCTs are identified for a particular intervention, then non-randomised comparative studies will be included. If no comparative data is available, then single-arm studies reporting pre- and post-treatment outcomes related to CGRP antagonists will be included.

7.4.1 Data extraction

One reviewer will independently extract data (on a trial-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:

- trial information: trial-arm, trial identifier, location, date, number of institutions, study design, length of follow-up, inclusion/exclusion criteria, study author
- demographic information: number of participants, age, sex, comorbidities, indication, disease history (i.e. number of years), migraine condition (type of migraine, intensity, frequency, average duration), body mass index, highest level of education, smoking status, alcohol status, caffeine intake
- intervention and comparator: drug name, dose, frequency of administration, concomitant and prior treatments/interventions (both pharmacological and non-pharmacological)
- outcomes of interest: event rates at baseline, final or change from baseline scores in any of the aforementioned outcomes (***Table 2***)
- any noteworthy features (i.e. effect modifiers), limitations or differences in the studies.

For studies that reported outcomes graphically, *WebPlotDigitizer* will be used to estimate numerical values.[40]

7.4.2 Assessment of quality of evidence

The assessment of the quality of evidence will be performed by one reviewer and checked by a second reviewer. Any differences will be settled via consensus. If consensus cannot be reached, a third reviewer will be consulted. Study quality and risk of bias will be assessed using different tools depending on the

trial design. RCTs will be evaluated using the Cochrane risk-of-bias tool version 2 (RoB 2.0),[41] non-randomised studies will be evaluated using the Cochrane ROBINS-I tool,[42] and single-arm trials will be evaluated using the Institute of Health Economics (IHE) quality appraisal checklist for case series.[43]

The overall quality of the evidence will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[44,45] The GRADEpro Guideline Development Tool (GDT) will be used to construct the summary of evidence tables.[46] 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.

7.4.3 Data analyses of efficacy, effectiveness and safety outcomes

Data on each CGRP antagonist will be analysed separately. Similarly, data on each class of comparator will be grouped separately. Only direct comparative evidence will be considered. Network or indirect analyses are outside the scope of this review.

Meta-analysis will be considered when at least 2 RCTs reporting the same outcome(s) in the same population, intervention and comparator group are identified. Pooling of data for meta-analysis will only be conducted when methodologically sound to do so.

If meta-analysis is not deemed to be appropriate, the results of this review will be reported narratively. Any meta-analyses will be conducted according to the methodology set out in ***Section 7.4.3.1*** of this protocol.

7.4.3.1 Meta-analysis methods

Dichotomous outcomes will be meta-analysed using ‘meta’ package in R Studio.[47-50] The meta-analysis will be performed using random-effects models with the Mantel-Haenszel statistical model. Results will be reported as risk ratios (RR) with 95% confidence intervals (CI).

Continuous outcomes will be meta-analysed using ‘meta’ package in R Studio.[47-50] The meta-analysis will be performed using random-effects models with the inverse variance method. Continuous outcomes will be reported as mean difference (MD) and/or standardised mean difference (SMD), which will be used to account for differences in the measurement scales reported for outcomes across included studies. The MDs will be interpreted as clinically important based on minimum clinical important differences (MCIDs) (not yet identified). Where an MCID is not defined for an outcome, only the statistical significance will be reported, and caution will be recommended in the interpretation of the reported result. The SMDs will be interpreted following the recommendations detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*, whereby a SMD of 0.2 represents a small effect, 0.5

a moderate effect, and 0.8 a large effect.[51] The random-effects model will be used to account for variations in population-based factors and discrepancies in how the intervention and comparators are delivered in the included trials.

For continuous outcomes, data will be pooled at specific timepoints. For each dichotomous outcome, the total number of events at longest duration of follow-up will be extracted and used in the meta-analysis; however, where dichotomous outcome data is too heterogenous to pool at longest duration of follow-up, data will be pooled at specific timepoints.

7.4.3.2 Assessment of heterogeneity

Meta-analysis results will be illustrated using forest plots, as they provide a visual representation of the reported effect sizes and uncertainty across the included studies. Heterogeneity and inconsistency will also be assessed statistically. The statistical methods that will be used to measure heterogeneity in meta-analyses of continuous outcomes are Tau^2 and I^2. Statistical methods that will be used to measure heterogeneity in meta-analyses of dichotomous outcomes is the Chi^2 test ($p < 0.10$ indicated significant heterogeneity) and I^2. The significance of I^2 will be dependent on the strength of the evidence for heterogeneity (i.e. Tau^2 and Chi^2) as well as direction and size of the measured effect. It will be interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*.[51] An I^2 of 0–40% is low (i.e. may not be important), 30–60% is moderate, 50–90% is substantial and 75–100% is considerable heterogeneity.[51]

7.4.3.3 Subgroup and sensitivity analyses

Data for each of the populations will be analysed separately. Additionally, for each population, interventions will be analysed separately and will be compared to each class of comparator (e.g. placebo, beta blockers, calcium antagonist) as a separate analysis.

As per the PICO criteria (***Table 2***), a broad population of chronic and episodic migraine sufferers has been included to ensure all available evidence is identified to address the research question. Additional subgroups have also been included that seek to capture the conditions for reimbursement of CGRP antagonists in Switzerland (***Appendix A***). Therefore, where evidence has been identified to meet the specific population for reimbursement in Switzerland, subgroup analyses will be conducted to investigate outcomes which meet the PICO criteria (see ***Table 2***).

Additional subgroup and sensitivity analyses may be conducted to investigate the impact of possible treatment-effect modifiers on the reported results (e.g. patient characteristics [age, comorbidities] and treatment regimen [dosage, timing, administration]), noting that this is not the focus of the policy question.

7.4.3.4 Assessment of publication bias

Publication bias in the meta-analysis will be assessed using funnel plots.[52] This method requires a minimum of 10 studies per outcome.[52]

7.4.3.5 Missing values

Missing standard deviations (SD) will be obtained from available means, sample sizes, standard errors (SE) and 95% CIs (for samples over 100 participants) using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*.[51]

$$SD = \sqrt{N}\ x\ (upper\ limit - lower\ limit)/3.92$$

Where continuous values need to be combined, formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)* will be used:[51]

$$Sample\ size = N_1 + N_2$$

$$Mean = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2\ 2M_2 M_2)}{N_1 + N_2 - 1}}$$

For studies that report outcomes graphically, *WebPlotDigitizer* will be used to convert graph points into numerical values.[40]

7.5 Economic evaluation

The HTA will investigate the cost-utility of CGRP antagonists (erenumab [Aimovig®], fremanezumab [Ajovy®] and galcanezumab [Emgality®], eptinezumab [Vyepti®])[1] for the prevention of migraine compared to the current standard of care. Current standard of care includes beta blockers (propranolol, metoprolol), calcium antagonists (flunarizine), anticonvulsants (topiramate), and antidepressants (amitriptyline). The intervention and comparator for the base case economic evaluation will be guided by the availability and quality of evidence identified during the clinical evaluation. Additional

[1] These medicines have been approved by the Swiss Agency for Therapeutic Products (Swissmedic) and are conditionally listed on the Spezialitätenliste.

comparisons, not identified during the clinical evaluation as having high-quality evidence, could be included as sensitivity analyses.

7.5.1 Methodological considerations for an independent economic evaluation

7.5.1.1 Population

Where evidence is available, the evaluation will consider patients who suffered from episodic migraine for at least one year and who did not respond or who insufficiently responded to at least 2 other migraine prevention therapies (such as beta blockers, calcium antagonists, anticonvulsants or the antidepressant amitriptyline) and patients who suffered from chronic migraine for at least one year and who did not respond or who insufficiently responded to at least 2 other migraine prevention therapies. In the absence of available evidence, a broader population (as described in ***Section 5.1***) of chronic and episodic migraine will be considered. Patient characteristics in the identified studies will be compared to the Swiss context during the evaluation phase. Characteristics will include considerations such as age, gender, baseline MMDs and medications. Clinical factors will include patient eligibility, duration of treatment or differences with associated health services, such as physician visits.

7.5.1.2 Intervention

The interventions in this HTA will include CGRP antagonists for the prevention of migraine, which include erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®).

7.5.1.3 Comparator

The comparator to be included in the economic evaluation will include the current standard of care for migraine prevention, which includes beta blockers (propranolol, metoprolol), calcium antagonists (flunarizine), anticonvulsants (topiramate) and antidepressants (amitriptyline), in the event this data is available. The decision as to what evidence to use in the economic evaluation will be made during the evaluation phase. The most robust level of evidence from RCTs or meta-analyses will be preferred.

7.5.1.4 Outcome

The proposed approach is a cost-utility analysis (CUA) from a Swiss healthcare payer perspective. EuroQol 5-dimension (EQ-5D) outcomes sourced from trials in the clinical evaluation section will be the preferred source for utility estimates in the economic evaluation. If they are not reported, other quality of life (QoL) data based on migraine-specific instruments and questionnaires (i.e. Migraine-Specific Quality of Life questionnaire [MSQ] and Headache Impact Test [HIT-6]) may be used and translated to EQ-5D outcomes, or EQ-5D utility data identified in the literature mapped to health states. The cost impacts of the intervention compared to the comparator will also be considered. If clinical evidence is

available, the model will examine the benefits from the prevention of chronification and costs and clinical outcomes associated with overuse headaches, long-term comorbidities such as depression or anxiety and adverse events from high use of analgesics (e.g. dialysis). Incremental cost-effectiveness ratios (ICERs) will be expressed as the cost per quality-adjusted life years (QALY) gained.

7.5.1.5 Proposed methodology

The systematic literature searches outlined in ***Table 4***, ***Appendix B*** will be used to identify economic studies from which an appropriate model could be used in the study and populated with Swiss data. Relevant economic studies will be assessed using the Drummond criteria for determining the quality of economic evaluations during the evaluation phase.[53] The exact nature of the model will be confirmed during the evaluation phase.

The proposed methodology for the economic evaluation will be aligned with published models. An overview of the proposed modelling methodology is provided in ***Table 3***. The model will be developed using TreeAgePro (TreeAge Software, Inc.)[54] and used for the base case and comparisons included for sensitivity analyses. Cost inputs will be sourced from Swiss diagnosis-related group (DRG) costs, the Swiss Spezialitätenliste[2] for medicines costs and TARMED positions. Costs and QALYs will be discounted at 3% per annum in the base analysis. Relevant model inputs such as probabilities will be derived from evidence identified in the clinical evaluation.

Probabilistic sensitivity analysis will be undertaken to account for uncertainty in the input parameters. The analysis will include 10,000 iterations to calculate a 95% CI. The probability of the ICER being cost-effective will be based on a hypothetical willingness-to-pay threshold of CHF100,000. The analysis will also show the effect of different price scenarios (i.e. price discount of 0–100%) on the ICER for the base case. Cost-effectiveness acceptability curves will be presented as part of sensitivity analyses, along with results based on differing time horizon, discount rates, medicine prices, unit costs, clinical input and QoL estimates.

Perspective

Table 3 Summary of the proposed economic evaluation methodology

Perspective	Swiss healthcare payer[2]

[2] The analysis will be performed from a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance will be analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

Patient population	• Patients who suffer from episodic migraine for at least one year who do not respond or who insufficiently responded to at least 2 other prevention therapies • Patients who suffer from chronic migraine for at least one year and who did not respond or who insufficiently responded to at least 2 other prevention therapies
Intervention	• Erenumab (Aimovig®) • Fremanezumab (Ajovy®) • Galcanezumab (Emgality®) • Eptinezumab (Vyepti®)
Comparator	Current standard of care. Cost-utility will also be estimated between the different CGRP antagonists
Type of economic evaluation	CUA
Time horizon	1, 5 and 10 years and possible additional horizons in sensitivity analyses
Sources of inputs	Published meta-analyses, RCTs, observational studies, Spezialitätenliste, TARMED, Swiss diagnosis-related group (DRG), expert opinion. EQ-5D weights will be sourced from clinical evidence or literature review.
Costs	Direct medical costs (CHF) (Pharmaceutical costs; laboratory costs; outpatient and inpatient medical care costs)
Effect measure	QALYs
Discount rate	3% p.a. for both costs and QALYs. 0 and 6% as sensitivity analyses.

Abbreviations
CGRP = calcitonin gene-related peptide, **CHF** = Swiss francs, **CUA** = cost-utility analysis, **DRG** = diagnosis-related group, **EQ-5D** = EuroQol 5-dimension questionnaire, **p.a.** = per annum, **RCT** = randomised control trial, **QALYs** = quality-adjusted life years

7.5.2 Budgetary impact analysis

Projected costs (CHF) to the payer from the use of CGRP antagonists for the prevention of migraine over the next 5 years under current policy/practice conditions will be evaluated. Budget impact analysis will be conducted to examine the financial implications for different reimbursement scenarios. Usage data for Switzerland for the intervention and comparator drugs will be sourced from © COGE GmbH Tarifpool © SASIS AG.[25] Key assumptions will be summarised in an evidence table that proceeds the base results. Sensitivity analyses will be included for major assumptions.

8 References

1. Swissmedic. ElViS Electronic Vigilance Reporting Portal 2021 [Available from: https://www.swissmedicinfo.ch/?Lang=EN accessed October 2021].
2. Bundesamt für Gesundheit BAG. Spezialitätenliste (SL) 2021 [Publikation vom 1. Oktober 2021:[Available from: http://www.xn--spezialittenliste-yqb.ch/ShowPreparations.aspx].
3. Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *The Journal of Headache and Pain* 2010;11(4):289-99.
4. Stovner LJ, Nichols E, Steiner TJ, et al. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2018;17(11):954-76.
5. Mungoven TJ, Henderson LA, Meylakh N. Chronic Migraine Pathophysiology and Treatment: A Review of Current Perspectives. *Frontiers in Pain Research* 2021;2(52)
6. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1-211.
7. Clinical Expert (Anonymised). CGRP-antagonists for the prevention of migraine: Questions for clinical experts. In: RACS, ed., 2021.
8. Merikangas KR, Cui L, Richardson AK, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. *BMJ* 2011;343:d5076.
9. Vo P, Paris N, Bilitou A, et al. Burden of Migraine in Europe Using Self-Reported Digital Diary Data from the Migraine Buddy© Application. *Neurol Ther* 2018;7(2):321-32.
10. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol* 2012;19(5):703-11.
11. Stovner LJ, Andrée C. Impact of headache in Europe: a review for the Eurolight project. *J Headache Pain* 2008;9(3):139-46.
12. Diener H-C, Holle-Lee D, Nägel S, et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. *Clinical and Translational Neuroscience* 2019;3(1):2514183X18823377.
13. Ha H, Gonzalez A. Migraine Headache Prophylaxis. *Am Fam Physician* 2019;99(1):17-24.
14. Miller S. The acute and preventative treatment of episodic migraine. *Ann Indian Acad Neurol* 2012;15(Suppl 1):S33-S39.
15. Andrée C, Barone-Kaganas IB, S, Böttger K, et al. Therapieempfehlungen für primäre Kopfschmerzen. *Schweizerische Kopfwehgesellschaft SKG* 2021;Auflage 10.1, vollständig überarbeitet
16. Diener H-C, Gaul C, Kropp P. Therapie der Migräneattacke und Prophylaxe der Migräne. *Nervenheilkunde* 2018;37(10):689-715.
17. Diener HC, Ashina M, Durand-Zaleski I, et al. Health technology assessment for the acute and preventive treatment of migraine: A position statement of the International Headache Society. *Cephalalgia* 2021;41(3):279-93.
18. Antonaci F, Dumitrache C, De Cillis I, et al. A review of current European treatment guidelines for migraine. *The Journal of Headache and Pain* 2010;11(1):13-19.
19. Andreou AP, Fuccaro M, Lambru G. The role of erenumab in the treatment of migraine. *Therapeutic Advances in Neurological Disorders* 2020;13:1756286420927119.
20. Mavridis T, Deligianni CI, Karagiorgis G, et al. Monoclonal Antibodies Targeting CGRP: From Clinical Studies to Real-World Evidence—What Do We Know So Far? *Pharmaceuticals* 2021;14(7):700.

21. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients – a review of pros and cons. *The Journal of Headache and Pain* 2017;18(1):96.

22. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. *Headache* 2006;46 Suppl 1(Suppl 1):S3-S8.

23. Vyepti. Highlights of prescribing information 2022 [Available from: https://www.lundbeck.com/content/dam/lundbeck-com/americas/united-states/products/neurology/vyepti_pi_us_en.pdf].

24. Tariq N. Which Anti-CGRP Antibody to Choose First for Chronic Migraine: NEJM Journal Watch; 2019 [Available from: https://www.jwatch.org/na48093/2019/01/02/which-anti-cgrp-antibody-choose-first-chronic-migraine].

25. COGE GmbH, Tarifpool SASIS AG. Cost data: CGRP-antaginists, 2021.

26. National Headache Foundation. Beta blockers USA2021 [Available from: https://headaches.org/2007/10/25/beta-blockers/ accessed October 2021].

27. Health Products Regulatory Authority. Sibelium 5mg tablet, 2020.

28. FDA. TOPAMAX (Topiramate) Tablets, TOPAMAX (Topiramate) Sprinkle Capsules, 2009.

29. Garza I, Swanson JW. Prophylaxis of migraine. *Neuropsychiatr Dis Treat* 2006;2(3):281-91.

30. Keizer RJ, Huitema AD, Schellens JH, et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet* 2010;49(8):493-507.

31. Ailani J, Burch RC, Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache* 2021;61(7):1021-39.

32. Drugbank. Propranolol 2021 [Available from: https://go.drugbank.com/drugs/DB00571 accessed October 2021].

33. Drugbank. Metoprolol 2021 [Available from: https://go.drugbank.com/drugs/DB00264 accessed October 2021].

34. Drugbank. Flunarizine 2021 [Available from: https://go.drugbank.com/drugs/DB04841 accessed October 2021].

35. Janssen Pharmaceuticals. Highlights of prescribing information 2022 [cited 2022 22 Febuary]. Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TOPAMAX-pi.pdf].

36. Drugbank. Amitriptyline 2021 [Available from: https://go.drugbank.com/drugs/DB00321 accessed October 2021].

37. Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz, et al. Rayyan — a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210.

38. Federal Chancellery. Romansh: Federal Chancellery; [Available from: https://www.bk.admin.ch/bk/en/home/regierungsunterstuetzung/languages/translation/raetoromanisch.html accessed March 19 2020].

39. Swiss Broadcasting Corporation. Languages: Swiss Broadcasting Corporation; 2019 [Available from: https://www.swissinfo.ch/eng/languages/29177618 accessed March 19 2020].

40. Ankit Rohatgi. WebPlotDigitizer: Ankit Rohatgi; 2021 [Available from: https://automeris.io/WebPlotDigitizer/ accessed October 2021].

41. Sterne J, Savović J, Page M, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366

42. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.(doi):10.1136/bmj.i4919.

43. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist Edmonton (AB): Institute of Health Economics; 2014 [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].

44. 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.

45. Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations: The GRADE Working Group, 2013.

46. McMaster University. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]: Evidence Prime, Inc.; [Available from: gradepro.org accessed October 2021].

47. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: Foundation for Statistical Computing, 2020.

48. RStudio Team. RStudio: Integrated Development for R. Boston, USA: RStudio, 2020.

49. Schwarzer G. General Package for Meta-Analysis. Version 4.18–0 2021 [Available from: https://cran.r-project.org/web/packages/meta/meta.pdf].

50. Schwarzer G, Carpenter J, Rücker G. Meta-Analysis with R2015.

51. Higgins JPT, J.; Chandler, J.; Cumpston, M.; Li, T; Page, M.J.; Welch, V.A. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). *Cochrane* 2021

52. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol* 2011;64(12):1277-82.

53. Drummond MF, O'Brien BJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press 1997.

54. TreeAge Software, version R1.1 [program]. Williamstown, MA; sofware available at https://www.treeage.com/, 2021.

55. INAHTA. INAHTA MEMBERS LIST 2022 [Available from: https://www.inahta.org/members/members_list/].

9 Appendices

9.1 Appendix A: Conditions for CGRP antagonist reimbursement in Switzerland

Overview of the coverage conditions of erenumab, fremanezumab, galcanezumab and eptinezumab according to the Spezialitätenliste[2]:

1. The treatment needs a confirmation of coverage after prior consultation with the medical officer.
2. A neurologist has to make the diagnosis, prescribe the antibody and supervise the follow-up monitoring.
3. Patients have to suffer for at least one year from either chronic or episodic migraines and their attacks have to be documented for at least 3 months. Chronic migraine patients have to experience migraines with attacks that last at least 4 hours on at least 15 days per month. Episodic migraine patients have to experience migraines with attacks that last at least 4 hours on at least 8 days per month. Their attacks have to be characterised by an aura or strong pain intensity combined with severe nausea/vomiting or severely debilitating photo- or phonophobia.
4. Patients have to be pre-treated with at least 2 prophylactic therapies such as beta blockers, calcium antagonists, anticonvulsants or amitriptyline for at least 3 months each. Patients have to either respond insufficiently to the prophylactic therapies or the prophylactic therapies are contraindicated for the patient or they had to be discontinued due to documented and clinically relevant side effects. (An insufficient treatment response is defined as no reduction of a minimum of 50% compared of days with migraines under treatment with one of the prophylactic therapies compared to prior to therapy beginning.)
5. In order for the treatment to be continued after 3 months, the average number of days with migraines have to be reduced compared to prior to the treatment begin and the reduction has to be documented in a migraine journal. In order for the treatment to be continued after 6 months, the average number of days with migraines have to be reduced by at minimum 50% compared to prior to the treatment begin and the reduction hast to be documented in a migraine journal.
6. In case of an insufficient or decreasing response to the treatment with either erenumab, galcanezumab, fremanezumab or eptinezumab, treatment with the other 2 is not reimbursed.

Appendix B: Literature search strategy

Table 4 Search strategy (PubMed)

Population	1.	Migraine*[tw]	43,321
	2.	Migraine[MeSH Term]	29,843
	3.	Headache*[tw]	103,843
	4.	Episodic migraine*[tw]	1,363
	5.	Chronic migraine*[tw]	2,733
	6.	**#1 OR #2 OR #3 OR #4 OR #5**	**125,977**
Intervention	7.	Calcitonin gene-related peptide*[tw]	16,362
	8.	Calcitonin gene-related peptide[MeSH Term]	12,026
	9.	CGRP*[tw]	10,667
	10.	Fremanezumab[tw]	199
	11.	TEV48125[tw] OR TEV 48125[tw] OR TEV-48125[tw]	23
	12.	Galcanezumab[tw]	237
	13.	LY2951742[tw]	34
	14.	Erenumab[tw]	342
	15.	AMG334[tw] OR AMG 334[tw] OR AMG-334[tw]	23
	16.	Eptinezumab[tw] OR eptinezumab-jjmr[tw]	104
	17.	ALD403[tw]	20
	18.	**#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**	**17,432**
Search string	**19.**	**#6 AND #18**	**2,312**

Abbreviations
CGRP = calcitonin gene-related peptide

9.2 Appendix C: HTA agency websites

Table 5 HTA agency websites

HTA Websites	
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
Russian Federation	
Center for Healthcare Quality Assessment and Control (CHQAC)	www.rosmedex.ru
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
Uruguay	
Health Assessment Division, Ministry of Public Health (HAD)	http://www.msp.gub.uy

Source:
Based on the INAHTA members list[55]

9.3 Appendix D: Study inclusion and exclusion criteria

Table 6 Study inclusion and exclusion criteria

Population 1	Patients who suffer from episodic migraine (i.e. characterised by less than 15 headache days per month)[6] *Exclusion criteria: Paediatric patients‡*
Population 2	Patients who suffer from chronic migraine (i.e. characterised by 15 or more headache days per month, for 3 months or more, with at least 8 migraine days per month)[6] *Exclusion criteria: Paediatric patients‡*
Intervention(s)	• Erenumab (Aimovig®)—70 or 140 mg once monthly • Fremanezumab (Ajovy®)—225 mg once monthly or 675 mg quarterly • Galcanezumab (Emgality®)—120 mg once monthly (starting dose of 240 mg) • Eptinezumab (Vyepti®)—100 mg or 300 mg quarterly *Exclusion criteria: Other CGRP antagonists (e.g. gepants), combination therapy with more than one intervention/comparator*

Comparator(s)	• Placebo
	• Standard of care for migraine prevention
	  ○ Beta blockers: propranolol, metoprolol
	  ○ Calcium antagonist: flunarizine
	  ○ Anticonvulsants: topiramate
	  ○ Antidepressants: amitriptyline
	• Other CGRP antagonists (i.e. comparing each of the interventions to each other)
	Exclusion criteria: Other beta blockers, calcium antagonists, anticonvulsants and antidepressants not listed here and/or not reimbursed in Switzerland

Outcome(s)	**Clinical outcomes:** • Monthly migraine days (MMDs) and monthly headache days (MHDs) • Health-related and migraine-specific quality of life (e.g. HIT-6, MSQ v2.1, MIDAS, TPB, EQ-5D, SF-36) • Migraine/headache pain intensity (e.g. VAS, NRS) • Number of days per month with a migraine that needs to be treated with acute pain relievers (i.e. MMDs with acute medication use) • Response rate (defined as a reduction of the average number of days with migraines of at least 50% after 6 months of treatment compared to prior to the treatment beginning) • Treatment adherence • Mortality • Treatment-related adverse events (AEs) • Serious adverse events (SAEs) • Adverse events leading to discontinuation • Adverse events upon discontinuation of CGRP antagonists (e.g. rebound effect) **Health-economic outcomes:** • Costs, utilities, ICER and budget impact
Design	**Studies will be selected based on the following hierarchy of study design, with preference given for the highest level of evidence.** **Effectiveness and safety outcomes:** • RCTs > non-randomised comparative studies > single-arm studies reporting pre- and post-treatment results Note: Inclusion of studies with ≥50 participants (all study designs) **Health-economics outcomes:** • RCTs > non-randomised comparative studies > single-arm studies reporting pre- and post-treatment results Note: Inclusion of studies with ≥50 participants (all study designs) *Exclusion criteria: case reports, conference abstracts, letter to the editors, expert opinions, editorials, review articles, non-human/laboratory studies, studies with <50 participants*
Country	No restriction
Year	RCTs: 10-year limit Non-RCTs: 5-year limit
Language	English, French, German and Italian

Abbreviations

AEs = adverse events, **CGRP** = calcitonin gene-related peptide, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test, **ICER** = incremental cost-effectiveness ratio, **MHDs** = monthly headache days, **MIDAS** = Migraine Disability Assessment Scale, **MMDs** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NRS** = numerical rating scale, **RCT** = randomised control

trial, **SAEs** = serious adverse events, **SF-36** = 36-Item Short Form Health Survey, **TPB** = total pain burden, **UK** = United Kingdom, **USA** = United States of America, **VAS** = visual analogue scale, **WHO** = World Health Organisation.

Notes

‡ As per expert advice, CGRP antagonists are not authorised for use in paediatric patients.[7]