MIGRAINE

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Migraine/Headache

Clinical Guidance- Issued April 2020

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

5-HT1F	5-Hydroxytryptamine (Serotonin) Receptor 1F
AE	Adverse Event
CABG	Coronary Artery Bypass Grafting
CADTH	Canadian Agency for Drugs and Technologies in Health
CGRP	Calcitonin Gene-Related Peptide
CHI	Council of Health Insurance
CHM	Commission on Human Medicines
CPG	Clinical Practice Guideline
CT	Computed Tomography
DHE	Dihydroergotamine
EHF	European Headache Federation
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HIS	International Headache Society
HTA	Health Technology Assessment
ICHD-3	International Classification of Headache Disorders, 3rd edition.
IDF	CHI Drug Formulary
IM	Intramuscular
IQWIG	Institute for Quality and Efficiency in Health Care
IV	Intravenous
KSA	Kingdom of Saudi Arabia
mAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
MOH	Medication-overuse headache
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTCP	Sodium-Taurocholate Cotransporting Polypeptide
OATP1B3	Organic Anion-Transporting Polypeptide 1B3
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PICO	Patients; Intervention; Comparison and Outcome
RCT	Randomized Controlled Trial
SC	Subcutaneous
SFDA	Saudi Food and Drug Authority
TIA	Transient Ischemic Attack

Executive Summary

Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting[1], and, frequently, cutaneous allodynia[2–5].

Migraine attacks can significantly impair functional ability at work or school, at home, and in social situations[6–8]. It ranks second worldwide, among neurologic conditions, in terms of years lost to disability[9,10]. and it is associated with a considerable financial burden, with annual total costs estimated at $27 billion in the United States[11,12].

In the Kingdom of Saudi Arabia (KSA), prevalence of migraine headache was originally reported from a 1997 survey of 22,630 individuals at 5%, with authors suggesting that the low figure relative to other population-based surveys possibly being affected by a skew towards the younger age of the sample, traditional lifestyles, and cultural differences in KSA[13]. More recently, a country wide cross-sectional survey with 2,421 respondents found migraine headache to have 1-year prevalence of 32% with an odds ratio (OR) = 1.9 for female gender[14]. In addition, specific to the population of Saudi Arabia, situational contexts contribute to burden. For example, fasting for approximately one month during the month of Ramadan ("first of Ramadan") can contribute to headache exacerbation along with the effects of dehydration and caffeine withdrawal[15].

Migraine is frequently mistaken for tension-type headache[16]. The International Classification of Headache Disorders criteria for migraine require only 2 of the 4 commonly seen pain characteristics, which means that a bilateral and non-throbbing headache can meet the criteria for migraine if it is moderate to severe, worsens with physical activity, and has the appropriate migraine accompanying features. Neck pain and provocation by stress, which are sometimes thought to be associated with tension-type headache, are common features of migraine as well[17].

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to migraine. The primary goal of the Council of Health Insurance (CHI) in issuing migraine guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with migraine in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on Saudi, American, European, and English guidelines issued within the last five years.

The management of migraine involves a multidisciplinary approach to reduce the pain, associated symptoms, and disability associated with attacks. Suboptimal acute treatment is associated with higher migraine-related disability and risk of disease progression[18].

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Migraine.

This report functions as an addendum to the prior CHI Migraine report and seeks to offer guidance for the effective management of migraine.

Regarding the management of migraine, several new drugs were approved by the FDA for treatment as well as for preventive treatment. No changes or modifications were made to existing drugs. However, it is worth noting that three drugs previously used in Saudi Arabia are no longer registered with the SFDA: Amitriptyline, Nortriptyline, and Tolfenamic acid.

Below is a table summarizing the major changes based on the different Migraine guidelines used to issue this report:

Table 1. General Recommendations for the Management of Migraine

Management of Migraine		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Diagnoses of migraine can be refined based on the frequency of monthly migraine days and monthly headache days based on ICHD-3 criteria for migraine and chronic migraine.	Not graded	The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice, 2021[19]
Use nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (e.g., aspirin + acetaminophen + caffeine) for mild-to- moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE], small-molecule CGRP receptor antagonists [gepants], selective serotonin (5-HT1F) receptor agonist [ditan]) for moderate or severe attacks and mild-to moderate attacks that respond poorly to nonspecific therapy.	Not graded	The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice, 2021[19]
For acute treatment of Migraine with or without	Not graded	Headaches in over 12s: diagnosis and

Aura: For people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated: • Consider a non-oral preparation of metoclopramide or prochlorperazine and • If non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID or triptan if they have not been tried.		management, Clinical guideline Published: 19 September 2012 Last updated: 17 December 2021[20]
In individuals with episodic migraine: eptinezumab, erenumab, fremanezumab and galcanezumab are recommended as preventive treatment.	Quality of evidence: moderate to high Strength of the recommendation: strong	European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update[21]
In individuals with chronic migraine, eptinezumab, erenumab, fremanezumab and galcanezumab are recommended as preventive treatment.	Quality of evidence: moderate to high Strength of the recommendation: strong	European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update[21]
In individuals with episodic or chronic migraine, erenumab is recommended over topiramate as preventive treatment.	Quality of evidence: low Strength of the recommendation: strong	European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update[21]

Section 3 lists the key recommendations synthesis for migraine treatment.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI migraine report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the updated versions of the guidelines mentioned in the 2020 CHI migraine report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
NICE guidelines of Headaches in over 12s: diagnosis and management [published 2012 last updated 2015]	**NICE** Clinical Guideline: Headaches in over 12s: diagnosis and management, Clinical guideline Published: 19 September 2012 Last updated: 17 December **2021**
Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults [2012] Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society	The **American Headache Society** Consensus Statement: Update on integrating new migraine treatments into clinical practice, **2021**
Management of Adults with Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies [2016]	
Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines [2016]	
Aids to management of headache disorders in primary care (2nd edition) on behalf of the European Headache Federation and Lifting. The Burden: The Global Campaign against Headache [2019]	**European Headache Federation** guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – **2022** update
European Headache Federation guidelines for Current and emerging evidence-based	

treatment options in chronic migraine: a narrative review [2019] ACUTE TREATMENT	
Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society [2019]	N/A*
Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society [2019]	N/A*

N/A: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 NICE Guidelines: Headaches in Over 12s: Diagnosis and Management (2021)

The National Institute for Health and Care Excellence (NICE) guidelines were updated from 2012 to 2021.

This guideline covers advice on the diagnosis and management of tension-type headache, migraine (including migraine with aura and menstrual-related migraine), cluster headache, and medication overuse headache in young people (aged 12 years and older) and adults. It aims to improve the recognition and management of headaches, with more targeted treatment to improve the quality of life for people with headaches, and to reduce unnecessary investigations[20].

- In May 2021, NICE amended recommendations on topiramate for migraine prophylaxis to include discussion of the potential benefits and risks, and the importance of effective contraception for women and girls of childbearing potential when taking topiramate.

Diagnosis:

Tension-type headache, migraine (with or without aura) and cluster headache:

Chronic migraine and chronic tension-type headache commonly overlap. If there are any features of migraine, diagnose chronic migraine.

Table 3. Headache Features According to Headache Type

Headache feature	Headache feature	Headache feature	Headache feature
Location (can be in the head, face, or neck)	Bilateral	Unilateral or bilateral	Unilateral (around the eye, above the eye and along the side of the head/face)
Pain quality	Pressing/tightening (non-pulsating)	Pulsating (throbbing or banging in young people aged 12 to 17 years)	Variable (can be sharp, boring, burning, throbbing, or tightening)
Pain intensity	Mild or moderate	Moderate or severe	Severe or very severe
Effect on activities	Not aggravated by routine activities of daily living	Aggravated by, or causes avoidance of, routine activities of daily living	Restlessness or agitation
Other Symptoms	None	Unusual sensitivity to light and/or sound or nausea and/or vomiting. Symptoms of aura can occur with or without headache and: • are fully reversible, • develop over at least 5 minutes, • last 5 to 60 minutes. Typical aura symptoms include visual symptoms such as flickering lights, spots, or lines and/or partial loss of vision; sensory symptoms such as numbness and/or pins and needles; and/or speech disturbance	On the same side as the headache: • red and/or watery eye • nasal congestion and/or runny nose • swollen eyelid • forehead and facial sweating • constricted pupil and/or drooping eyelid

Duration of Headache	30 minutes to continuous	4 to 72 hours in adults 1 to 72 hours in young people aged 12 to 17 years	15 to 180 minutes

Episodic tension-type headaches occur on fewer than 15 days per month. Chronic tension-type headaches occur on 15 or more days per month for more than 3 months.

Episodic migraines (with or without aura) occur on fewer than 15 days per month. Chronic migraines (with or without aura) occur on 15 or more days per month for more than 3 months.

Episodic cluster headaches occur from once every other day to 8 times a day with a pain-free period of more than 1 month. Chronic cluster headaches occur from once every other day to 8 times a day with a continuous pain-free period of less than 1 month in a 12-month period. [2012]

Migraine with aura:

Suspect aura in people who present with or without headache and with neurological symptoms that:

- Are fully reversible and
- Develop gradually, either alone or in succession, over at least 5 minutes and last for 5 to 60 minutes. [2012]

Diagnose migraine with aura in people who present with or without headache and with one or more of the following typical aura symptoms that meet the criteria in the above recommendation:

- Visual symptoms that may be positive (for example, flickering lights, spots, or lines) and/or negative (for example, partial loss of vision)
- Sensory symptoms that may be positive (for example, pins and needles) and/or negative (for example, numbness)
- Speech disturbance. [2012]

Consider further investigations and/or referral for:

- Motor weakness or
- Double vision or
- Visual symptoms affecting only one eye or
- Poor balance or
- Decreased level of consciousness. [2012]

Diagnosis: menstrual-related migraine

Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles. [2012]

Diagnose menstrual-related migraine using a headache diary for at least 2 menstrual cycles. [2012]

Medication overuse headache

Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:

- Triptans, opioids, ergots, or combination analgesic medications on 10 days per month or more or
- Paracetamol, aspirin or an NSAID, either alone or in any combination, on 15 days per month or more. [2012]

The updated recommendations are listed below:

For acute treatment of Migraine with or without Aura: For people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated:

- Consider a non-oral preparation of metoclopramide or prochlorperazine and
- If non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID or triptan if they have not been tried. [2021]

Note the special warnings and precautions for use for metoclopramide and prochlorperazine and discuss the benefits and risks with the person (or their parents or carers, as appropriate).

For the prophylaxis of migraine, offer topiramate or propranolol after a full discussion of the benefits and risks of each option. Include in the discussion:

- The potential benefit in reducing migraine recurrence and severity
- The risk of fetal malformations with topiramate
- The risk of reduced effectiveness of hormonal contraceptives with topiramate
- The importance of effective contraception for women and girls of childbearing potential who are taking topiramate (for example, by using medroxyprogesterone acetate depot injection, an intrauterine method or combined hormonal contraception with a barrier method).

In the context of the known harms with valproate, the Commission on Human Medicines (CHM) has reviewed available safety data relating to the use of other key antiepileptic drugs in pregnancy for the risk of major congenital

malformations, neurodevelopmental disorders and delay, and other effects on the baby. The key antiepileptic drugs were selected for the review based on their place in UK clinical practice[22].

On this basis, data on the use of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide in pregnancy were reviewed:

Major congenital malformations: The review of risk of major congenital malformations assessed data from meta-analyses of epidemiological studies and other large epidemiological studies. The studies reviewed include comparisons of pregnancy outcomes between women given antiepileptic drug monotherapy and women without epilepsy or women with epilepsy who were not treated with antiepileptic drugs.

- For lamotrigine (more than 12,000 pregnancies exposed) and levetiracetam (more 1,800 pregnancies exposed): data do not suggest an increased risk of major congenital malformations when these antiepileptic drugs are used at the usual maintenance doses.

  For lamotrigine: one study showed a statistically significant increase in the rate of major congenital malformations when doses of lamotrigine higher than 325mg per day were compared with doses of lamotrigine 325mg per day or lower.

  Other studies do not suggest dose-response effect on the risk of major congenital malformations.

- Carbamazepine, phenobarbital, phenytoin, and topiramate: are associated with an increased risk of major congenital malformations compared with that seen in the general population and women with epilepsy not on an antiepileptic drug the risk of major congenital malformations with carbamazepine, phenobarbital, and topiramate is dose dependent.

- The available data for pregabalin suggest it may be associated with a slightly increased risk of major congenital malformations, but these data include emerging findings that are currently under review and further evaluation is needed to reach definitive conclusions.

- Due to limitations of the data for gabapentin, oxcarbazepine, and zonisamide, the risk remains uncertain; the possibility of an increased risk of major congenital malformations can neither be confirmed nor ruled out.

Neurodevelopmental disorders and delay

The review also considered meta-analyses and epidemiological studies that investigated the risk of adverse effects on neurodevelopmental outcomes including measures of intelligence, developmental outcomes, and symptoms or diagnoses of autism spectrum disorders in children exposed in-utero to antiepileptic drugs.

These data support the following conclusions:

- For carbamazepine, lamotrigine, and levetiracetam, data do not suggest an increased risk of neurodevelopmental disorders or delay, however, due to the limitations of these data the possibility of an increased risk cannot be definitively ruled out.
- For phenobarbital and phenytoin, although the clinical studies report inconsistent findings, the totality of the data shows the possibility of adverse effects on neurodevelopment.
- Some recent data raise concerns that topiramate use during pregnancy may be associated with poorer developmental outcomes, however, the numbers in the available studies remain limited and further data are needed to reach firm conclusions.
- For gabapentin, oxcarbazepine, pregabalin, and zonisamide, the data are either lacking, extremely limited, or have limitations, and the risks remain uncertain.

1.1.2 The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice (2021)

In 2021, the American Headache Society published a Consensus Statement on the use of newly introduced treatments for adults with migraine. This update, which is based on the expanded evidence base and emerging expert consensus concerning post-approval usage, provides practical recommendations in the absence of a formal guideline.

The 2021 American Headache Association guideline listed the below recommendations[19]:

Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting and, frequently, cutaneous allodynia.

About one third of those with migraine have migraine with aura, and approximately three quarters experience a premonitory phase prior to the onset of headache.

Diagnoses of migraine can be refined based on the frequency of monthly migraine days and monthly headache days. Criteria are listed in the table below:

Table 4. ICHD-3 Criteria for Migraine and Chronic Migraine

Migraine
(A) At least five attacks fulfilling criteria B–D
(B) Headache attacks lasting 4–72 h (when untreated or unsuccessfully treated)
(C) Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
(D) During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
(E) Not better accounted for by another diagnosis
Chronic Migraine
(A) Migraine-like or tension-type-like headache on ≥15 days/month for >3 months that fulfill criteria B and C
(B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura
(C) On ≥8 days/month for >3 months, fulfilling any of the following: 1. Criteria C and D for migraine without aura 2. Criteria B and C for migraine with aura 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
(D) Not better accounted for by another diagnosis
Abbreviation: ICHD-3, International Classification of Headache Disorders, 3rd edition.

1. Acute Treatment

Use nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics,

acetaminophen, or caffeinated analgesic combinations (e.g., aspirin + acetaminophen + caffeine) for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE], small-molecule CGRP receptor antagonists [gepants], selective serotonin (5-HT1F) receptor agonist [ditan]) for moderate or severe attacks and mild-to- moderate attacks that respond poorly to nonspecific therapy.

Newly introduced acute treatments include: two small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists (ubrogepant, rimegepant); a serotonin (5-HT1F) agonist (lasmiditan); a nonsteroidal anti-inflammatory drug

(celecoxib oral solution); and a neuromodulatory device (remote electrical neuromodulation).

New preventive treatments include an intravenous anti-CGRP ligand monoclonal antibody (eptinezumab).

Acute treatments considered effective or probably effective based on reviews of available evidence are listed in the table below:

Table 5. Acute Treatments with Evidence of Efficacy in Migraine

Established efficacy	Probably effective
Migraine-specific	
Triptans	Ergotamine
Ergotamine derivatives	Other forms of dihydroergotamine
Gepants	
Lasmiditan	
Nonspecific	
NSAIDs: aspirin, celecoxib oral solution, diclofenac, ibuprofen, naproxen	NSAIDs: flurbiprofen, ketoprofen, IV and IM ketorolac
Combination analgesic: acetaminophen + aspirin + caffeine	IV magnesium
	Isometheptene-containing compounds
	Antiemetics: chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine

A nonoral formulation should be used in patients whose attacks are associated with severe nausea or vomiting, who do not respond well to traditional oral treatments, or who have trouble swallowing orally administered medications.

This includes sumatriptan 3, 4, or 6 mg subcutaneous (SC) and intranasal liquid and powder formulations, as well ketorolac in intranasal and intramuscular (IM) formulations.

Alternatives include DHE SC and intranasal spray. Intravenous (IV) DHE and an antiemetic should be considered especially for refractory headaches. In addition, antiemetics, such as prochlorperazine and promethazine suppositories (for both headache and nausea), may be useful.

Other nonoral options for acute treatment include neuromodulatory devices. Nonoral routes of administration should also be considered in patients who do not respond well to traditional oral treatments or experience significant nausea or vomiting early during attacks.

Tolerability and safety of certain acute treatments may preclude usage in many patients including those with certain coexistent or comorbid illnesses.

- NSAIDs can cause serious gastrointestinal and cardiovascular side effects.
- Triptans and ergot derivatives should be avoided or used with caution in patients with coronary artery disease, peripheral vascular disease, uncontrolled hypertension, and other vascular risk factors and disorders.

  In patients with preexisting vascular disease or in whom triptans are otherwise contraindicated, gepants, ditans, or neuromodulatory devices may be useful.

Considering self-administered rescue

When acute treatment does not bring relief, patients may require rescue medication. Depending on the initial treatment:

- Options for outpatient rescue include SC sumatriptan, DHE IM or intranasal spray, IM ketorolac, or corticosteroids (e.g., dexamethasone)
- Office-based or inpatient options may include parenteral formulations of triptans, DHE, antiemetics, NSAIDs (e.g., ketorolac), anticonvulsants (e.g., valproate sodium [not in women of childbearing potential who are not using an appropriate method of birth control), corticosteroids, magnesium sulfate, and peripheral nerve blocks. Consider recommending a self-administered rescue treatment for patients with severe attacks and those who have a history of nonresponse or variable response to acute treatment.

2. Preventive Treatment

Patients with migraine should be considered for preventive treatment in any of the following situations:

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as follows:
  a. Ten or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
  b. Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs
- AEs with acute treatments
- Patient preference

Preventive treatment plans must be designed to meet the needs of individual patients with migraines. Table 6 shows preventive pharmacologic treatments that are effective or probably effective based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence.

Table 6. Medications with Evidence of Efficacy in Migraine Prevention

Established efficacy		Probably effective	
Oral	**Parenteral**	**Oral**	**Parenteral**
Candesartan	Eptinezumab	Amitriptyline	OnabotulinumtoxinA + CGRP mAb
Divalproex sodium	Erenumab	Atenolol	
Frovatriptan	Fremanezumab	Lisinopril	
Metoprolol	Galcanezumab	Memantine	
Propranolol	OnabotulinumtoxinA	Nadolol	
Timolol			Venlafaxine
Topiramate			
Valproate sodium			

Oral treatments should be started at a low dose and titrated slowly until the target response develops, the maximum or target dose is reached, or tolerability issues emerge.

With oral treatments, an initial target dose should be set (e.g., topiramate 100 mg) and patients advised to stop the titration if the maximal dose is reached, when efficacy is optimal, or when AEs become intolerable.

With injectable treatments (i.e., on a botulinum toxin A or any of the CGRP mAbs): patients often experience a rapid onset of therapeutic benefits, but the duration of the transition from established preventive treatment to CGRP mAb (i.e., the interim period when both treatments are taken) has not been defined.

Because treatment response in migraine is highly individualized, the decision to stop taking established therapies should rely on assessment of the onset and magnitude of treatment effects with the CGRP mAb at 4, 8, and 12 weeks after treatment with both therapies begins. There is data to suggest continued improvement beyond 3 months.

1.1.3 European Headache Federation Guideline on the Use of Monoclonal Antibodies Targeting the Calcitonin Gene Related Peptide Pathway for Migraine Prevention – 2022 Update

The previous European Headache Federation (EHF) guideline addressed the use of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway to prevent migraine. Since then, randomized controlled trials (RCTs) and real-world evidence have expanded the evidence and knowledge for those treatments. Therefore, the EHF panel decided to provide an updated guideline on the use of those treatments.

This guideline is structured into two parts; the first part reports the evidence-based recommendations, and the second part reports the Expert Consensus Statements:

For the evidence-based recommendations: Clinical questions were developed according to the GRADE system as Patients; Intervention; Comparison and Outcome (PICO). Three PICO questions were addressed, and outcomes are delignated in the table below:

Table 7. EHF Evidence-Based Recommendations for Prevention of Migraine

Question	Outcome from RCTs	Evidence based recommendation
In individuals with episodic migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway as compared to placebo, effective and safe?	Reduction in migraine days, responder rate (individuals with migraine with at least 50% reduction in migraine days), reduction in the use of acute attack medication, safety (serious adverse events or mortality)	In individuals with episodic migraine: eptinezumab, erenumab, fremanezumab and galcanezumab are recommended as preventive treatment. **Quality of evidence: moderate to high; Strength of the recommendation: strong**
In individuals with chronic migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway as compared to placebo, effective and safe?	Reduction in migraine days, responder rate (individuals with migraine with at least 50% reduction in migraine days), reduction in the use of acute attack medication,	In individuals with chronic migraine, EHF recommends eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment.

	safety (serious adverse events or mortality)	**Quality of evidence: moderate to high** **Strength of the recommendation: strong**
In individuals with migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway, as compared to another migraine preventive treatment, more effective and/or tolerable?	Reduction in migraine days, responder ratio (individuals with migraine with at least 50% reduction in migraine days), reduction in the use of acute attack medication, discontinuation, due to adverse events, safety (serious adverse events or mortality)	In individuals with episodic or chronic migraine EHF recommends erenumab over topiramate as preventive treatment. **Quality of evidence: low** **Strength of the recommendation: strong**

For expert consensus statements

The summary of statements is reported below:

- In individuals with migraine who require preventive treatment, it was suggested that monoclonal antibodies targeting the CGRP pathway to be included as a first line treatment option.
- In individuals with episodic or chronic migraine there is insufficient evidence to make suggestions regarding the combination of monoclonal antibodies targeting the CGRP with other preventatives to improve migraine clinical outcomes.
- In individuals with episodic or chronic migraine who start a new treatment with one monoclonal antibody targeting the CGRP pathway, evaluating efficacy after a minimum of 3 consecutive months on treatment was suggested.
- In individuals with episodic or chronic migraine, it was suggested to consider a pause in the treatment with monoclonal antibodies targeting the CGRP pathway after 12-18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, it was suggested to restart the treatment if migraine worsens after treatment withdrawal.
- In individuals with migraine and medication overuse, offering monoclonal antibodies targeting the CGRP pathway is suggested.

- In individuals with migraine with inadequate response to one monoclonal antibody targeting the CGRP pathway, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option.
- It was suggested to avoid monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women. We suggest caution and decision on a case-by-case basis in the presence of vascular disease or risk factors and Raynaud phenomenon. We suggest caution in erenumab use in individuals with migraine with history of severe constipation.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Migraine report, along with their recommendations.

Table 8. List of Additional Guidelines

Additional Guidelines
2015 Saudi guidelines: Migraine Headache: Diagnosis & Management
Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine, A national clinical guideline. First published February 2018, Revised March 2023.

1.2.1 Saudi Guidelines: Migraine Headache: Diagnosis & Management (2015)

There are recommendations published by Saudi clinical guidelines for Migraine management 2015 below[23]:

Diagnosis recommendation:

The panel recommends that clinicians do not use head MRI or CT imaging in patients with migraine or suspected of migraine that do not have other indications for imaging. (Strong recommendation, very low-quality evidence).

Acute Pharmacological Management

- The panel suggests either metoclopramide or a NSAID in patients with acute migraine. (Conditional recommendation, very low-quality evidence). The panel determined that there is not enough evidence to favor one over the other.
- The panel suggests metoclopramide rather than a triptan in patients with acute mi-graine. (Conditional recommendation, low quality evidence)
- The panel suggests a triptan rather than paracetamol in patients with acute migraine. (Conditional recommendation, very low-quality evidence).
- The panel suggests a combination of a triptan with a NSAID rather than a NSAID alone in patients with acute migraine. (Conditional recommendation, low quality evidence).

- The panel suggests a combination of a triptan with a NSAID rather than a triptan alone in patients with acute migraine. (Conditional recommendation, very low-quality evidence).

Prophylactic Pharmacological Management

- The panel suggests using beta-blockers for the prevention of migraine attacks. (Conditional recommendation, low quality evidence).
- The panel suggests topiramate 50 to 100 mg daily for the prevention of migraine attacks. (Conditional recommendation, moderate quality evidence)
- The panel suggests valproate 500 to 1000 mg daily for the prevention of migraine attacks. (Conditional recommendation, low quality evidence).
- The panel suggests that clinicians use either topiramate or beta-blockers for the prevention of migraine attacks. (Conditional recommendation, low quality evidence).
- The panel suggests triptans for the prevention of menstrual-related migraine attacks. (Conditional recommendation, low quality evidence).
- The panel recommends that clinicians do not use botulinum toxin A for the prevention of migraine attacks in patients with episodic migraine. (Strong recommendation, moderate quality evidence).
- The panel suggests botulinum toxin A injections for the prevention of chronic migraine in patients who have not responded to other prophylactic treatments. (Conditional recommendation, low quality evidence).
- The panel suggests tricyclic antidepressants for the prevention of migraine attacks. (Conditional recommendation, low quality evidence).
- The panel suggests that clinicians do not use SSRIs for the prevention of migraine attacks until more evidence is available. (Conditional recommendation, low quality evidence).

Prophylactic Non-Pharmacological Management

- The panel suggests that more research is done on the effectiveness and cost-effectiveness of education and self-management programs. (Conditional recommendation, very low-quality evidence).

1.2.2. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine, A national clinical guideline. First published February 2018, Revised March 2023.

This guideline provides recommendations based on current evidence for best practice in the acute and prophylactic management of adults with migraine using pharmacological therapies or devices. The focus is on adults with acute migraine and preventative treatment in patients with episodic or chronic

migraine and medication-overuse headache. Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine[24].

DEFINITIONS

According to the international classification of headache disorders (ICHD) Migraine is subdivided into migraine with and without aura. It is defined as episodic and chronic.

Episodic migraine occurs on less than 15 days per month and can be further subdivided into low frequency (1–9 days per month) and high frequency (10–14 days per month).

Chronic migraine Chronic migraine occurs on 15 or more days per month.

The majority of patients with chronic migraine have background headache with superimposed migraine attacks.

A consensus statement was produced in 2007 with a new definition of chronic migraine and this has been used in all subsequent studies on chronic migraine. Chronic migraine is now defined as headache on 15 or more days per month with superimposed migraine on eight or more days per month, for more than three months.

This has been further refined in the ICHD beta 3 edition to allow migraine attacks to be with and without aura and also to include attacks that the patient believes are migraine and respond to acute treatment for migraine.

Medication-overuse headache (MOH) is defined as headache on 15 or more days per month that has evolved along with the frequent use of acute medication, for more than three months.

TREATMENT

Medical treatment is subdivided into acute and preventative.

Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack.

It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response.

Preventative treatment is taken continuously in order to reduce the frequency and severity of migraine attacks.

Often a combination of acute and preventative treatment is needed.

For treatment to be effective, it is crucial that the correct diagnosis has been made. Choice of treatment should take account of severity and frequency of attacks, other symptoms, patient preference, history of treatment and comorbid conditions.

Patients have a variable response to triptans and it is worth sequencing through the triptans to find the most effective treatment.

When starting a preventative treatment, a low dose should be used and treatment dose gradually increased.

The minimum effective dose should be used and this may vary between patients.

The need for ongoing prophylaxis should be considered after six to 12 months.

ACUTE TREATMENT

Aspirin (900 mg) is recommended as first-line treatment for patients with acute migraine.

Ibuprofen (400 mg) is recommended as first-line treatment for patients with acute migraine. If ineffective, the dose should be increased to 600 mg.

Paracetamol (1,000 mg) can be considered for treatment of patients with acute migraine who are unable to take other acute therapies.

Due to its safety profile, paracetamol is first choice for the short-term relief of mild to moderate headache during any trimester of pregnancy.

Metoclopramide (10 mg) or prochlorperazine (10 mg) can be considered in the treatment of headache in patients with acute migraine. They can be used either as an oral or parenteral formulation depending on presentation and setting.

Metoclopramide (10 mg) or prochlorperazine (10 mg) should be considered for patients presenting with migraine-associated symptoms of nausea or vomiting. They can be used either as an oral or parenteral formulation depending on presentation and setting.

Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects.

Triptans are recommended as first-line treatment for patients with acute migraine. The first choice is sumatriptan (50–100 mg), but others should be offered if sumatriptan fails.

Triptans are recommended for the treatment of patients with acute migraine associated with menstruation.

Sumatriptan can be considered for treatment of acute migraine in pregnant women in all stages of pregnancy. The risks associated with use should be discussed before commencing treatment.

Combination therapy using sumatriptan (50–85 mg) and naproxen (500 mg) should be considered for the treatment of patients with acute migraine.

No evidence was identified on the use of prednisolone as a tapered treatment in patients with prolonged migraine (>3 days).

PREVENTION OF MIGRAINE

Propranolol (80–160 mg daily) is recommended as a first-line prophylactic treatment for patients with episodic or chronic migraine.

Topiramate (50–100 mg daily) is recommended as a prophylactic treatment for patients with episodic or chronic migraine.

Before commencing treatment, women should be informed of:

- the risks associated with taking topiramate during pregnancy
- the risk that potentially harmful exposure to topiramate may occur before a woman is aware she is pregnant
- the need to use highly-effective contraception.
- the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.

Amitriptyline (25–150 mg at night) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

In patients who cannot tolerate amitriptyline a less sedating tricyclic antidepressant should be considered.

Candesartan (16 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Use of candesartan should be avoided during pregnancy and breastfeeding. Women using candesartan who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.

Sodium valproate (400–1,500 mg daily) can be considered as a prophylactic treatment for patients over the age of 55 with episodic or chronic migraine.

Valproate is not recommended for those under the age of 55 for those who remain on it and who fulfil MHRA requirements, the safety advice is to inform the patient of the risks to children exposed to valproate in utero and the need to use effective contraception.

Flunarizine (10 mg daily) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Use of flunarazine should be avoided during pregnancy and breastfeeding. Women using flunarazine who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.

Gabapentin should not be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and

patients have been appropriately treated with three or more oral migraine prophylactic treatments.

Botulinum toxin A should only be administered by appropriately trained individuals under the supervision of a headache clinic or the local neurology service.

Erenumab, fremanezumab, galcanezumab and eptinezumab are recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Fremanezumab, galcenezumab and eptinezumab can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Use of CGRP monoclonal antibodies should only be initiated following consultation with a neurologist or headache specialist.

There should be careful consideration of potential risks and benefits to patients at high risk of ischaemic cardiovascular disease before prescribing CGRP monoclonal antibodies.

Use of CGRP monoclonal antibodies should be avoided during pregnancy and breastfeeding. A washout period of 6 months is advised before trying for a pregnancy.

Medication overuse headache should be addressed before treatment with CGRPs. However, in patients where treatment of MOH has been unsuccessful, CGRP monoclonal antibodies should still be considered.

MENSTRUAL MIGRAINE PROPHYLAXIS

Frovatriptan (2.5 mg twice daily) should be considered as a prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.

Zolmitriptan (2.5 mg three times daily) or naratriptan (2.5 mg twice daily) can be considered as alternatives to frovatriptan as prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.

Women with menstrual-related migraine who are using triptans at other times of the month should be advised that additional perimenstrual prophylaxis increases the risk of developing medication overuse headache.

MEDICATION-OVERUSE HEADACHE

In patients overusing acute treatment, medication overuse should be addressed.

When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache.

The choice of strategy to address medication overuse should be tailored to the individual patient and may be influenced by comorbidities.

Strategies include:

- Abrupt withdrawal alone and preventative treatment may then be considered after a delay
- Abrupt withdrawal and immediately starting preventative treatment y starting a preventative treatment without withdrawal.

Consider withdrawing regular opioids gradually.

Prednisolone should not be used routinely in the management of patients with medication-overuse headache.

Section 2.0 Drug Therapy in Migraine

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA but are not currently SFDA registered.

2.1 Additions

Several treatments were recently approved for the treatment and prevention of Migraine. Four drugs are registered by the SFDA including erenumab and galcanezumab for the **prevention** of migraine, and ubrogepant and Lasmiditan for the **treatment** of migraine. Detailed information of these drugs is described below.

2.1.1 Erenumab

Erenumab (AIMOVIG®) is a calcitonin gene-related peptide receptor antagonist approved by FDA in 2018 and indicated for the preventive treatment of migraine in adults. Main characteristics are listed in the table below:

Table 9. Drug Therapy with Erenumab

SCIENTIFIC NAME ERENUMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes, 2018
EMA	Yes, 2018
MHRA	NO
PMDA	NO
Indication (ICD-10)	G43
Drug Class	CGRP inhibitors / Human Monoclonal Antibody
Drug Sub-class	CGRP inhibitors
ATC Code	N02CD01
Pharmacological Class (ASHP)	CGRP Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled pen
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	For subcutaneous use only:

	- Recommended dosage is 70 mg once monthly; some patients may benefit from a dosage of 140 mg once monthly. - The 140 mg dose is administered once monthly as two consecutive injections of 70 mg each. - Administer in the abdomen, thigh, or upper arm subcutaneously
Maximum Daily Dose Adults*	140 mg once monthly
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	No dosage adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh A or B). It has not been studied in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended.
Prescribing edits*	AGE, ST, PA, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches (to be restricted to neurology consultants)	

PA (Prior Authorization):
• Approved for prevention of migraine only if:
  o Patient has 4 or more migraine days a month
  o At least 3 preventive drug treatments have failed
• For patients without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina, or CABG).
• To be used with caution in patients with hypertension.	

QL (Quantity Limit): N/A	
ST (Step Therapy): Approved for use after failure to at least three prophylactic treatments and without cardiovascular disease	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common adverse reactions in AIMOVIG clinical studies (occurring in at least 3% of treated patients and more often than placebo) are injection site reactions and constipation. A 2020 systematic review evaluating the adverse reactions to erenumab reported instances of back pain, influenza, nasopharyngitis, and upper respiratory tract infections, albeit with significant heterogeneity[25].
Drug Interactions*	None
Special Population	Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.
Pregnancy	Outcome data following maternal use of erenumab during pregnancy are limited. The risk of hypertensive disorders, including preeclampsia and eclampsia, are also increased in pregnant patients with migraine. In general, preventive treatment for migraine should be avoided during pregnancy.
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AIMOVIG and any potential adverse effects on the breastfed infant from AIMOVIG or from the underlying maternal condition.
Contraindications	Serious hypersensitivity (eg, angioedema, anaphylaxis) to erenumab or any component of the formulation
Monitoring Requirements	Blood pressure

Precautions	Hypertension and worsening of preexisting hypertension have been reported.
Black Box Warning	None
REMS*	Not Applicable

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations of Erenumab (Aimovig®) by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). Key conclusions and recommendations are listed per verbatim from their original source.

Table 10. Erenumab HTA Analysis

Medication	Agency	Date – HTA Recommendation
Erenumab	CADTH[26]	2020: The Canadian Drug Expert Committee **recommends that erenumab be reimbursed** for the prevention of chronic migraine in adults, if the following **conditions** are met. **Initiation criteria**: The patient has a confirmed diagnosis of chronic migraine according to the International Headache Society criteria, which defined it as headaches that last for at least 15 days per month for more than three months of which at least eight days per month are with migraine. The patient has experienced an inadequate response, intolerance, or contraindication to two or three oral prophylactic migraine medications. Patients who have had a lack of therapeutic response to four or more prior oral prophylactic migraine medications are not eligible for reimbursement. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement. The maximum duration of initial authorization is six months. **Renewal criteria**: The physician must provide proof of beneficial clinical effect when requesting continuation of

		reimbursement, defined as a reduction of at least 50% in the number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the number of migraine days per month has been maintained. The maximum duration of subsequent authorizations following the initial authorization is six months. As a prescribing conditions: The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches. CADTH also recommended that the **price must be reduced**.
	NICE[27]	2023: The cost-effectiveness estimates are within what NICE usually considers an **acceptable use of NHS resources**. Erenumab is recommended for preventing migraine in adults who have at least 4 migraine days per month. Erenumab is recommended as an option for preventing migraine in adults, only if: • they have 4 or more migraine days a month • at least 3 preventive drug treatments have failed • the 140 mg dose of Erenumab is used and • the company provides it according to the commercial arrangement. Nice also recommended to Stop Erenumab after 12 weeks of treatment if: • in episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50% • In chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%. These recommendations are not intended to affect treatment with Erenumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance

		was published, until they and their NHS clinician consider it appropriate to stop.
	HAS[28]	2022: Favorable opinion for reimbursement only in patients with severe migraine and at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, transient ischemic attack (TIA), unstable angina or coronary artery bypass graft (CABG)). Clinical benefit now substantial (previously it was moderate) in this indication considering the following elements: • severity of the disease and its prevalence, • the partially covered medical need in severe migraine situations (≥ 8 migraine days per month) after previous failure to at least two prophylactic treatments, with the need to have access to more effective prophylactic treatments with fewer adverse effects, • the lack of additional response to the identified need, with the absence of an additional impact on morbidity in severe migraine situations after failure to at least two prophylactic treatments, and the absence of new data in terms of the impact on quality of life in this chronic, incapacitating condition, • the absence of data relative to an additional impact on the care pathway of patients • AIMOVIG (erenumab) is unlikely to have an additional impact on public health. Considering all these elements, the Committee deems that the clinical benefit of AIMOVIG (erenumab) is high in patients with severe migraine and at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina, or CABG). The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved

		for use in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina, or CABG). **Recommended reimbursement rate: 65%**
	IQWIG[29]	2019: Erenumab was approved for both episodic and chronic migraine. The study results evaluated also do not have to be restricted to episodic migraine as the literature provides no medical or other substantive justification for the value of "14 days" to distinguish episodic from chronic migraine. In addition, the participants in the LIBERTY study were in the transition period between episodic and chronic migraine. Overall, IQWiG therefore sees an indication of a **considerable added benefit** of Erenumab for the prophylaxis of migraine.
	PBAC	**The pharmaceutical company has withdrawn their submission** for this medicine prior to the medicine being considered at the PBAC meeting. The process for listing this medicine has ceased.

Conclusion Statement – Erenumab

Erenumab is a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults. HTA recommendations for Erenumab were mostly favorable for the reimbursement of the medication, yet criteria for inclusion were set by CADTH, NICE and HAS (for eligible patients without associated risk vascular factors). At the same time, all HTA bodies recommended a price reduction or partial reimbursement.

Based on the above, we suggest considering adding Erenumab for prevention of migraine with prior authorization, conditional approval, and considering the inclusion criteria as set by HTA bodies. Close follow-up for response to therapy is recommended.

2.1.2 Galcanezumab

Galcanezumab is a calcitonin gene-related peptide receptor antagonist approved by FDA in 2018 and indicated for the preventive treatment of migraine in adults. Main characteristics are listed in the table below:

Table 11. Drug Therapy with Galcanezumab

SCIENTIFIC NAME GALCANEZUMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes, 2018
EMA	Yes, 2018
MHRA	Restricted use within NHSScotland, 2020
PMDA	Yes, 2021
Indication (ICD-10)	G43
Drug Class	CGRP inhibitors / Human Monoclonal Antibody
Drug Sub-class	CGRP inhibitors
ATC Code	N02CD02
Pharmacological Class (ASHP)	CGRP Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled pen
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	For subcutaneous use only. • Recommended dosage: 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg. • Administer in the abdomen, thigh, back of the upper arm, or buttocks subcutaneously.
Maximum Daily Dose Adults*	300 mg in a single dose
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	None
Prescribing edits*	AGE, ST, PA, MD

AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches (to be restricted to neurology consultants).	
PA (Prior Authorization): Conditional approval for patients who have 4 or more migraine days a month and at least 3 preventive drug treatments have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Approved for use after failure to at least three prophylactic treatments and without cardiovascular disease	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common adverse reactions (incidence ≥ 2% and at least 2% greater than placebo) in clinical studies were injection site reactions.
Drug Interactions*	None
Special Population	None
Pregnancy	There are no data on the developmental risks associated with this drug in human pregnancy; animal data have not shown adverse effects on embryofetal development.
Lactation	There are no data on the presence of galcanezumab-gnlm in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed infant or from the underlying maternal condition.
Contraindications	Contraindicated in patients with serious hypersensitivity to galcanezumab-gnlm or to any of the excipients.
Monitoring Requirements	None

Precautions	Hypersensitivity reactions: If a serious hypersensitivity reaction occurs, discontinue administration of EMGALITY and initiate appropriate therapy. Hypersensitivity reactions could occur days after administration and may be prolonged.
Black Box Warning	None
REMS*	Not Applicable

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations of galcanezumab by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). Key conclusions and recommendations are listed per verbatim from their original source.

Table 12. Galcanezumab HTA Analysis

Medication	Agency	Date – HTA Recommendation
Galcanezumab	CADTH[30]	2020: CADTH recommends that Emgality should be reimbursed by public drug plans for the prevention of migraine if certain conditions are met. It should only be covered to prevent migraine attacks in adult patients who have tried at least 2 other types of oral preventive medications. Emgality should only be reimbursed if the patient is being cared for by a physician who has experience managing migraine headaches. Emgality will only be reimbursed for 6 months at a time. Emgality should not be more than the least costly drug of the same class used to prevent migraine. Recommendation is based on Evidence from 4 clinical trials that demonstrated that Emgality reduced the frequency of migraine headache days, and migraine-related disability. Emgality may also reduce migraine intensity, the use of acute pain medication, and improve daily functioning and health-related quality of life.

		There is no evidence to suggest Emgality is more effective than other reimbursed therapies used to treat patients with migraines. Therefore, Emgality should be priced no more than the lowest cost alternative to ensure cost-effectiveness. Economic evidence suggests the price of Emgality must be reduced by approximately 49% to 78% to ensure Emgality is cost-effective at a $50,000 per quality-adjusted life-year (QALY) threshold.
	NICE[31]	2020: For episodic and chronic migraine, the most likely cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So galcanezumab is recommended for episodic and chronic migraine. Galcanezumab is recommended as an option for preventing migraine in adults, only if: • They have 4 or more migraine days/month • At least 3 preventive drug treatments have failed and • The company provides it according to the commercial arrangement. Stop galcanezumab after 12 weeks of treatment if: • In episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50% • In chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%. This recommendation is not intended to affect treatment with galcanezumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
	HAS[32]	2020: **Favorable opinion** for reimbursement in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without

		cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis (DVT) or other serious cardiovascular risk). The clinical benefit of EMGALITY (galcanezumab) is substantial in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis (DVT) or other serious cardiovascular risk). **Unfavorable opinion** for reimbursement in the rest of the MA indication: The clinical benefit of EMGALITY (galcanezumab) is insufficient to justify its funding by the French national health insurance system in other patients falling within the scope of the MA indication.
	IQWIG[33]	2019: There is an indication of major added benefit of Galcanezumab versus best supportive care (BSC) for adult patients who have at least 4 migraine days/month and for whom BSC is the only treatment option: Patients who do not respond to any of the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, clostridium botulinum toxin type A.
	PBAC	2022: The PBAC recommended amending the PBS listing of Galcanezumab for chronic migraine to include the treatment of patients with high frequency episodic migraine by removing the criteria for patients to have an average of 15 or more headache days per month. The resulting PBS listing for galcanezumab is for the treatment of patients who have an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications,

		with 8 or more migraine headache days per month. The PBAC considered galcanezumab would be cost effective for the high frequency episodic migraine patient population at a price no higher than the price for patients with chronic migraine.

Conclusion Statement – Galcanezumab

Galcanezumab is a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults). The clinical benefit according to HAS evaluation was substantial in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease. Similar recommendations were identified by NICE and IQWIG. Yet, CADTH opinion was not favoring reimbursement Emgality® of versus other effective therapies based on cost effectiveness concerns. the price of Emgality® must be reduced by approximately 49% to 78% to ensure it is cost-effective.

Based on the above, we suggest considering adding Emgality® for prevention of migraine with prior authorization, conditional approval and for eligible patients without associated cardiovascular risk factors, who have 4 or more migraine days a month and at least 3 preventive drug treatments have failed. Close follow-up for response to therapy is recommended.

2.1.3 Ubrogepant

In 2019, Ubrogepant was the first drug in the gepant class to receive FDA approval for the acute treatment of migraine and has shown efficacy in two randomized controlled clinical trials[19].

Table 13. Drug Therapy with Ubrogepant

SCIENTIFIC NAME UBROGEPANT	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	NO
MHRA	NO
PMDA	NO
Indication (ICD-10)	G43
Drug Class	Calcitonin gene-related peptide receptor antagonist
Drug Sub-class	CGRP inhibitors

ATC Code	N/A
Pharmacological Class (ASHP)	Calcitonin Gene-related Peptide (CGRP) Antagonists
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	The recommended dose is 50 mg or 100 mg taken orally, as needed. If needed, a second dose may be administered at least 2 hours after the initial dose.
Maximum Daily Dose Adults*	200 mg
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	Severe Hepatic or Severe Renal Impairment: Recommended dose is 50 mg; if needed, a second 50 mg dose may be taken at least 2 hours after the initial dose.
Prescribing edits*	AGE, MD, PA
AGE (Age Edit): Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. Safety and effectiveness in pediatric patients have not been established	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches (to be restricted to neurology consultants).	
PA (Prior Authorization): Indicated for the acute treatment of moderate to severe migraines with or without auras in adults. Not indicated for the prevention of migraine.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Nausea and somnolence.

Drug Interactions*	Strong CYP3A4 Inducers: Should be avoided as concomitant use will result in reduction of ubrogepant exposure. For additional dose modifications for moderate or weak CYP3A4 inhibitors and inducers or BCRP and/or P-gp only inhibitors.
Special Population	Pregnancy: Based on animal data, may cause fetal harm. Avoid use in patients with end-stage renal disease.
Pregnancy	Based on animal data, may cause fetal harm. Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant.
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed infant from UBRELVY or from the underlying maternal condition.
Contraindications	Concomitant use with strong CYP3A4 inhibitors
Monitoring Requirements	None
Precautions	Hypersensitivity reactions, including anaphylaxis, dyspnea, facial or throat edema, rash, urticaria, and pruritus, reported with use; hypersensitivity reactions can occur minutes, hours, or days after administration; most reactions occurred within hours after dosing and were not serious, and some reactions led to discontinuation; if serious or severe hypersensitivity reaction occurs, discontinue treatment and institute appropriate therapy
Black Box Warning	None
REMS*	N/A

Health Technology Assessment (HTA)

The Canadian Agency for Drugs and Technologies in Health (CADTH) was the only agency to evaluate UBRELVY® (ubrogepant). Key conclusions and recommendations are listed per verbatim from their original source in the table below:

Table 14. Ubrogepant HTA Analysis

Medication	Agency	Date – HTA Recommendation
Ubrogepant	CADTH[34]	2023: The evaluation by CADTH for Ubrogepant was negative based on the following: • No studies comparing the gepants to other acute treatment of migraine were identified and thus their relative efficacy and safety to the triptans and their place in therapy are unknown. The studies evaluated the gepants on a single episode of a migraine attack which did not permit the assessment of the consistency of the effects of the drugs over time. • Although the cost of the drugs in Canada is not available, it is likely to have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers. Clinical trials on ubrogepant excluded patients with clinically significant cardiovascular diseases. This raises concerns about the use of these drug in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases.
	NICE	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Ubrogepant

Ubrogepant was the first drug in the gepant class to receive FDA approval for the acute treatment of migraine but didn't get the approval for prevention of Migraine episodes. It was approved by the Saudi FDA and US FDA only. Based on the HTA evaluation of CADTH in 2023, there is no positive recommendation to include this medication for the treatment of Migraine as of yet.

2.1.4 Rimegepant

Nurtek ODT® (Rimegepant) is a calcitonin gene-related peptide receptor antagonist approved by FDA in 2020 and indicated for the acute treatment of migraine with or without aura in adults. Main characteristics are listed in the table below:

Table 15. Drug Therapy with Rimegepant

SCIENTIFIC NAME RIMEGEPANT	
SFDA Classification	N/A
SFDA Approval	No
US FDA	Yes, 2020
EMA	Yes, 2020
MHRA	NO
PMDA	NO
Indication (ICD-10)	G43
Drug Class	CGRP inhibitors / Human Monoclonal Antibody
Drug Sub-class	CGRP inhibitors
ATC Code	N02CD06
Pharmacological Class (ASHP)	CGRP Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Orally disintegrating tablets:
Route of Administration	Oral Use
Dose (Adult) [DDD]*	The recommended dose is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The safety of treating more than 15 migraines in a 30-day period has not been established.
Maximum Daily Dose Adults*	75 mg per day
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	
Prescribing edits*	AGE, MD, PA
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches (to be restricted to neurology consultants).
PA (Prior Authorization): 1. Attacks significantly interfere with patients' daily routines despite acute treatment. 2. Frequent attacks > 6 days or more per month 3. Contraindication to, failure, or overuse of acute treatments, with overuse defined as follows: **a.** Ten or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused. **b.** Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs. **4.** Adverse event with acute treatments.
QL (Quantity Limit): N/A
ST (Step Therapy): N/A
EU (Emergency Use Only): N/A
PE (Protocol Edit): N/A

SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common adverse reactions in AIMOVIG clinical studies (occurring in at least 3% of treated patients and more often than placebo) are injection site reactions and constipation
Drug Interactions*	Strong CYP3A4 Inhibitors: Avoid concomitant administration. Moderate CYP3A4 Inhibitors: Avoid another dose within 48 hours when administered with a moderate CYP3A4 inhibitor. Strong and Moderate CYP3A Inducers: Avoid concomitant administration. Inhibitors of P-gp or BCRP: Avoid concomitant administration
Special Population	Exposures were significantly higher in subjects with severe hepatic impairment. Avoid use in patients with severe hepatic impairment (Child-Pugh C).

Pregnancy	Not assigned
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NURTEC ODT and any potential adverse effects on the breastfed infant from NURTEC ODT or from the underlying maternal condition.
Contraindications	Patients with a history of hypersensitivity reaction to Rimegepant, or to any of its component.
Monitoring Requirements	None
Precautions	Hypersensitivity reactions: If a serious hypersensitivity reaction occurs, discontinue and initiate appropriate therapy. Severe hypersensitivity reactions have included dyspnea and rash, and can occur days after administration
Black Box Warning	None
REMS*	Not Applicable

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations of Rimegepan by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). Key conclusions and recommendations are listed per verbatim from their original source in the table below:

Table 16. Rimegepant HTA Analysis

Medication	Agency	Date – HTA Recommendation
Rimegepant	CADTH (2020)	2020: Two Gepants, Rimegepant and Ubrogepant, have completed phase III trials for the acute treatment of migraine. • No studies comparing the gepants to other acute treatment of migraine were identified and thus their relative efficacy and safety to

		the triptans and their place in therapy are unknown. The studies evaluated the gepants on a single episode of a migraine attack which did not permit the assessment of the consistency of the effects of the drugs over time. • Although the cost of the drugs in Canada is not available, it is likely to have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers. • Clinical trials on Rimegepant excluded patients with current evidence of uncontrolled, unstable, or recently diagnosed cardiovascular disease. This raises concerns about the use of these drug in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases. Further, clinical trials on Rimegepant also excluded patients with current diagnosis of major depression, a condition that is commonly comorbid with migraine.
	NICE[35]	2023: HTA recommendation for treatment of migraine will be published in October 2023. **For migraine prevention:** Rimegepant was considered as cost effective compared with 2 of the 3 usual treatments. So Rimegepant it was recommended for preventing migraine after 3 or more preventative treatments have not worked. - Rimegepant is recommended as an option for preventing episodic migraine in adults who have at least 4 and fewer than 15 migraine attacks per month, only if at least 3 preventative treatments have not worked. - It must be stopped after 12 weeks of treatment if the frequency of migraine attacks does not reduce by at least 50%. - If people with the condition and their clinicians consider Rimegepant to be 1 of a

		range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements. These recommendations are not intended to affect treatment with Rimegepant that was started in the NHS before this guidance was published.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Rimegepant

According to the Canadian Agency for Drugs and Technologies in Health (CADTH) which is the only organization who evaluated Rimegepant, there are concerns about the use of Rimegepant in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases. CADTH report also stated that clinical trials on Rimegepant excluded patients with current diagnosis of major depression, a condition that is commonly comorbid with migraine.

As a result, we do not suggest the inclusion of Rimegepant as of yet.

2.1.5 Lasmiditan

Lasmiditan is the first of a new group of headache medicines that are being called the "ditans. It is a serotonin (5-HT) 1F receptor agonist approved by FDA in 2019 for the acute treatment of migraine with or without aura in adults. Main characteristics are listed in the table below:

Table 17. Drug Therapy with Lasmiditan

SCIENTIFIC NAME LASMIDITAN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes, 2019
EMA	Yes, 2022
MHRA	NO
PMDA	NO
Indication (ICD-10)	G43
Drug Class	Ditan

Drug Sub-class	Serotonin (5-HT) 1F receptor agonist
ATC Code	None
Pharmacological Class (ASHP)	Selective Serotonin Agonists
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. No more than one dose should be taken in 24 hours
Maximum Daily Dose Adults*	200 mg
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	No dosage adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh A or B). It has not been studied in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended.
Prescribing edits*	AGE, MD, QL, PA, ST
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches (to be restricted to neurology consultants).	
PA (Prior Authorization): Only indicated for the acute treatment of migraine; not indicated for prevention. Has potential for abuse, and withdrawal treatment may be necessary in the setting of overuse. U.S. DEA schedule V controlled substance.	
QL (Quantity Limit): do not dispense for more than one month due to risk of abuse and dependence	
ST (Step Therapy): consider use if triptans are contraindicated (e.g., cardiovascular risk factors), ineffective, or poorly tolerated.	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reactions (≥5% and > placebo) were dizziness, fatigue, paresthesia, and sedation.
Drug Interactions*	May further lower heart rate when administered with heart rate lowering drugs. Avoid concomitant use with P-gp and Breast Cancer Resistant Protein (BCRP) substrates.
Special Population	Based on animal data, may cause fetal harm. It has not been studied in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended.
Pregnancy	Based on animal data, may cause fetal harm. Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant.
Lactation	Inform patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed.
Contraindications	None
Monitoring Requirements	None
Precautions	• Driving Impairment: Advise patients not to drive or operate machinery for at least 8 hours after taking each dose of Lasmiditan. Patients who cannot follow this advice should not take Lasmiditan. Patients may not be able to assess their own driving competence and the degree of impairment caused by Lasmiditan. • Central Nervous System (CNS) Depression: Lasmiditan may cause CNS depression and should be used with caution if used in combination with alcohol or other CNS depressants.

	• Serotonin Syndrome: Reactions consistent with serotonin syndrome were reported in patients treated with Lasmiditan. Discontinue if symptoms of serotonin syndrome occur. • Medication Overuse Headache: Detoxification may be necessary
Black Box Warning	None
REMS*	In 2019, the Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of lasmiditan outweigh its risks. Based on the safety profile and efficacy demonstrated in the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required[36].

Health Technology Assessment (HTA)

The Canadian Agency for Drugs and Technologies in Health (CADTH) was the only agency to evaluate REYVOW® (lasmiditan). Key conclusions and recommendations are listed per verbatim from their original source in the table below:

Table 18. Lasmiditan HTA Analysis

Medication	Agency	Date – HTA Recommendation
Lasmiditan	CADTH	2023: • There is potential for lasmiditan to be an alternative migraine treatment for patients who have failed, or have a contraindication, to triptans. Further studies are required to confirm the safety of Lasmiditan in patients with cardiovascular or cerebrovascular disease. • Due to frequent dizziness, the manufacturer recommends patients who take lasmiditan not engage in activities requiring mental alertness (e.g., driving) for at least eight hours. • Lasmiditan is also associated with euphoria and hallucinations, suggesting abuse potential.
	NICE	Appraisal suspended in 2022

	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Lasmiditan

Lasmiditan, the first drug in the ditan class to receive FDA approval for the acute treatment of migraine but didn't get the approval for prevention of Migraine episodes. It was approved by the Saudi FDA, EMA and US FDA. Lasmiditan is also associated with euphoria and hallucinations, suggesting abuse potential.

Lasmiditan is currently classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule V controlled substance. Substances in this schedule have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics[37]. Two individual commenters expressed concerns with DEA's placing lasmiditan in schedule V due to the overall lack of data for the drug's abuse and dependence risks. As a result, they believed schedule IV was more appropriate for this nascent drug, as a schedule IV classification provides more oversight by physicians for prescribing this drug to patients[38]. Based on this information, a "prior authorization (PA)" prescribing edit is recommended for the inclusion of Lasmiditan.

2.2 Modifications

There are no new modifications in the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

Tolfenamic acid was withdrawn from Saudi FDA for treatment of Migraine. Amitriptyline and Nortriptyline were both withdrawn from SFDA, however other TCAs remain available and SFDA registered.

2.4 Other Drugs

Several drugs were also approved for treatment and prevention of migraine and were evaluated by HTA organizations yet were **not registered by SFDA**. It remains vital to review the characteristics of these medications as some were approved based on reliable evidence supporting efficacy and safety.

2.4.1 Zavegepant

ZAVEGEPANT is a calcitonin gene-related peptide receptor antagonist approved by FDA in 2023 and indicated for the acute treatment of migraine with or without aura in adults. Main characteristics are listed in the table below:

Table 19. Drug Therapy with Zavegepant

SCIENTIFIC NAME ZAVEGEPANT	
SFDA Classification	N/A
SFDA Approval	No
US FDA	Yes, 2023
EMA	Yes, 2019
MHRA	Yes, 2021
PMDA	NO
Indication (ICD-10)	G43
Drug Class	CGRP inhibitors / Human Monoclonal Antibody
Drug Sub-class	CGRP inhibitors
ATC Code	N02CD03
Pharmacological Class (ASHP)	CGRP Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Nasal Spray
Route of Administration	Intranasal
Dose (Adult) [DDD]*	The recommended dose is 10 mg given as a single spray in one nostril, as needed. The maximum dose in a 24-hour period is 10 mg (one spray). The safety of treating more than 8 migraines in a 30-day period has not been established.
Maximum Daily Dose Adults*	10 mg
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	
Prescribing edits*	AGE, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches.	
PA (Prior Authorization): N/A	

QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reactions (at least 2% of patients treated with ZAVZPRET and greater than placebo) were taste disorders, nausea, nasal discomfort, and vomiting.
Drug Interactions*	Avoid use with drugs that inhibit organic anion-transporting polypeptide 1B3 (OATP1B3) or Sodium-taurocholate cotransporting polypeptide (NTCP) transporters. Avoid use with drugs that induce OATP1B3 or NTCP transporters. Avoid use of intranasal decongestants; if unavoidable, administer intranasal decongestants at least 1 hour after ZAVZPRET administration
Special Population	Avoid use in patients with severe hepatic impairment. Avoid use in patients with CrCl < 30 mL/min
Pregnancy	Not assigned
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZAVZPRET and any potential adverse effects on the breast-fed infant from ZAVZPRET or from the underlying maternal condition.
Contraindications	Patients with a history of hypersensitivity reaction to zavegepant or to any of the components of ZAVZPRET.
Monitoring Requirements	None
Precautions	Hypersensitivity Reactions: If a serious hypersensitivity reaction occurs, discontinue ZAVZPRET and initiate appropriate therapy. Hypersensitivity Reactions including facial swelling

	and urticaria have occurred with ZAVZPRET
Black Box Warning	None
REMS*	Not Applicable

Health Technology Assessment (HTA)

None of the health technology Assessment agencies/institutes/authorities including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), provided a recommendation for Zavegepant.

Conclusion Statement – Zavegepant

Zavegepant is a calcitonin gene-related peptide receptor antagonist. It is given via the intranasal route. It is not registered by SFDA, nor evaluated by HTA agencies. As a result, we do not suggest the inclusion of Zavegepant.

2.4.2 Atogepant

ATOGEPANT is a calcitonin gene-related peptide receptor antagonist approved by FDA in 2023. Main characteristics are listed in the table below:

Table 20. Drug Therapy with Atogepant

SCIENTIFIC NAME ATOGEPANT	
SFDA Classification	N/A
SFDA Approval	No
US FDA	Yes, 2021
EMA	Yes, 2023
MHRA	Yes, 2023
PMDA	NO
Indication (ICD-10)	G43
Drug Class	CGRP inhibitors
Drug Sub-class	CGRP inhibitors
ATC Code	N02CD01
Pharmacological Class (ASHP)	CGRP
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Migraine, chronic, prevention (alternative agent)**: Oral: 60 mg once daily.

	<u>Migraine, episodic, prevention (alternative agent):</u> Oral: 10 mg, 30 mg, or 60 mg once daily Note: For the prevention of episodic migraine, limit use to patients with <15 headache days per month.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Safety and effectiveness in pediatric patients have not been established.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	<u>Dosing: Kidney Impairment: Adult</u> <u>Migraine, chronic, prevention:</u> - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl <30 mL/minute: Avoid use. <u>Migraine, episodic, prevention:</u> - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl <30 mL/minute: 10 mg once daily. - Hemodialysis, intermittent (thrice weekly): 10 mg once daily; administer after dialysis on dialysis days. <u>Dosing: Hepatic Impairment: Adult</u> <u>Mild to moderate impairment (Child-Pugh class A, B):</u> - No dosage adjustment necessary. <u>Severe impairment (Child-Pugh class C):</u> - Use is not recommended.
Prescribing edits*	AGE, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): The patient should be under the care of a physician who has the appropriate qualifications and experience with the management of migraine headaches.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Weight loss, constipation, decreased appetite, nausea, dizziness, drowsiness, fatigue.
Drug Interactions*	Avoid use with erdafitinib, fexinidazole, fusidic acid (systemic), leniosilib, and taurursodiol.
Special Population	Avoid use in patients with severe hepatic impairment. Avoid use in patients with CrCl < 30 mL/min
Pregnancy	Adverse events were observed in animal reproduction studies following oral administration of atogepant in doses greater than the recommended human dose. Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. Based on animal data, CGRP may help regulate placental blood flow, uterine relaxation, and maintain BP; CGRP antagonists could potentially increase the risk of gestational hypertension and preeclampsia. The risk of hypertensive disorders, including preeclampsia and eclampsia, are also increased in pregnant patients with migraine
Lactation	It is not known if atogepant is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient.

	Oral calcitonin gene-related peptide receptor antagonists are not currently recommended for the prevention of migraine in lactating patients due to lack of data.
Contraindications	Hypersensitivity (eg, anaphylaxis, dyspnea) to atogepant or any component of the formulation.
Monitoring Requirements	Kidney and liver function (baseline and as clinically indicated). Anaphylaxis, dyspnea, facial edema, pruritus, rash, and/or urticaria may occur. Hypersensitivity reactions may occur days after administration. If a hypersensitivity reaction occurs, discontinue therapy and administer appropriate therapy. Hepatic impairment: Use is not recommended in patients with severe hepatic impairment. Renal impairment: Dose reduction or avoidance of use required in severe and end-stage renal impairment.
Precautions	Hypersensitivity Reactions.
Black Box Warning	None
REMS*	Not Applicable

Health Technology Assessment (HTA)

Table 21: HTA analysis of Atogepant

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Atogepant	NICE[5]	In development- Expected to be out in April 2024
	CADTH[6]	Positive reimbursement based on specific conditions: CADTH recommends that Qulipta be reimbursed by public drug plans for the prevention of episodic migraine, if certain conditions are met. Qulipta should only be reimbursed for adults with episodic migraine, according to the criteria used by public drug plans for other calcitonin gene related peptide (CGRP) inhibitors for the prevention of episodic migraine. In addition to following the pre-existing criteria for other CGRP inhibitors, Qulipta should not be used in

		combination with other CGRP inhibitors. Qulipta should only be reimbursed if the cost is reduced such that the total treatment cost of Qulipta does not exceed the total treatment cost of the least costly CGRP inhibitor reimbursed for the preventive treatment of episodic migraine in adults.
	HAS[7]	Favorable opinion for reimbursement only in the preventive treatment of migraine in adult patients suffering from severe migraine with at least 8 days of migraine per month, who have failed at least two prophylactic treatments and without cardiovascular disease (patients who have had cardiovascular disease or established cerebrovascular disease, with recent history (< 6 months) of acute coronary syndrome or stroke/TIA, or hypertension).
	IQWIG	No recommendations found.
	PBAC	No recommendations found.

Many clinical trials study the effect of atogepant in prevention of migraine in comparison to placebo.

Table 22: Primary literature studying atogepant

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Patricia Pozo-Rosich et al.	Atogepant for the Preventive Treatment of Migraine in Participants with Prior Treatment Failure: The **ELEVATE** Trial[1]	Evaluate the efficacy, safety, and tolerability of atogepant 60 mg once daily (QD) for the preventive treatment of EM in participants whose previous treatments failed to	The primary endpoint was change from baseline in mean MMDs across 12 weeks. Secondary endpoints included: – Achievement of ≥50% reduction in MMDs across 12 weeks	Among participants who had prior inadequate response to 2–4 classes of oral preventive medication, atogepant 60 mg QD resulted in a significantly greater reduction in MMDs

			help reduce the impact of migraine	– Change from baseline in Headache Impact Test-6 (HIT-6) total score at week 12 – Change from baseline in Migraine-Specific Quality of Life questionnaire Role Function–Restrictive (MSQ v2.1 RFR) domain score at week 12	compared with placebo across 12 weeks. Secondary endpoints of achievement of ≥50% reduction in MMDs across 12 weeks, reduction in HIT-6 total scores at week 12, and improvement in MSQ v2.1 RFR scores at week 12 also showed a statistically significant treatment effect for atogepant vs placebo. Atogepant 60 mg QD was well tolerated, and the safety results were consistent with the known safety profile of atogepant.
2	Messoud Ashina MD, PhD, DMSc,	Once-daily oral atogepant for the long-term preventive	To assess long-term safety, tolerability, and efficacy of once-daily	The primary outcome was safety and tolerability, which was assessed by	The trial included 744 participants randomized to atogepant 60 mg (n

	FEAN et al.	treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial[2]	oral atogepant 60 mg in adults with migraine.	monitoring AEs, clinical laboratory evaluations, vital sign measurements, ECG findings, and C-SSRS scores. Efficacy outcomes included change from baseline in mean MMDs, proportion of participants with reduction from baseline of least 50%, 75%, and 100% MMDs at weeks 1–4, 9–12, 21–24, 33–36, and 49–52, and change from baseline in mean monthly acute medication use days.	= 546) or SC (n = 198). The atogepant safety population was 88.2% female (n = 479/543) with a mean (standard deviation) age of 42.5 (12.0) years. TEAEs occurred in 67.0% (n = 364/543) of participants treated with atogepant 60 mg. The most commonly reported TEAEs (≥5%) were upper respiratory tract infection (10.3%; 56/543), constipation (7.2%; 39/543), nausea (6.3%; 34/543), and urinary tract infection (5.2%; 28/543). Serious TEAEs were reported in 4.4% (24/543) for atogepant. Mean (standard error) change in MMDs for

					atogepant was −3.8 (0.1) for weeks 1–4 and −5.2 (0.2) at weeks 49–52. Similarly, the proportion of participants with ≥50%, ≥75%, and 100% reductions in MMDs increased from 60.4% (310/513), 37.2% (191/513), and 20.7% (106/513) at weeks 1–4 to 84.2% (282/335), 69.9% (234/335), and 48.4% (162/335), at weeks 49–52. Daily use of oral atogepant 60 mg for preventive treatment of migraine during this 1-year, open-label trial was safe, well tolerated, and efficacious.
3	Jessica Ailani,	**ADVANCE** trial: Atogepant	The phase 3 trial (ADVANCE)	The primary efficacy end point was the	A total of 2270 participants were

	M.D. et al.	for the Preventive Treatment of Migraine[3]	examines the efficacy and safety of atogepant administered once daily at a dose of 10 mg, 30 mg, or 60 mg as compared with placebo for the prevention of migraine in participants with episodic migraine.	change from baseline in the mean number of migraine days per month across the 12-week treatment period (the average of month 1, month 2, and month 3) as recorded in the diaries or reported during visits. Secondary efficacy end points, which were tested in hierarchical order, were the change from baseline in the mean number of headache days per month across the 12-week treatment period; the change from baseline in the mean number of days of use of medication for the treatment of migraine attacks across the 12-week treatment	screened, 910 were enrolled, and 873 were included in the efficacy analysis; 214 were assigned to the 10-mg atogepant group, 223 to the 30-mg atogepant group, 222 to the 60-mg atogepant group, and 214 to the placebo group. The mean number of migraine days per month at baseline ranged from 7.5 to 7.9 in the four groups. The changes from baseline across 12 weeks were −3.7 days with 10-mg atogepant, −3.9 days with 30-mg atogepant, −4.2 days with 60-mg atogepant, and −2.5 days with placebo. The mean

				period; a reduction from baseline of at least 50% in the 3-month average of migraine days per month; the change from baseline in the score on the Role Function–Restrictive domain of the MSQ, version 2.1, at week 12; the change from baseline in the mean monthly score on the Performance of Daily Activities domain of the AIM-D across the 12-week treatment period; and the change from baseline in the mean monthly score on the Physical Impairment domain of the AIM-D across the 12-week treatment period.	differences from placebo in the change from baseline were −1.2 days with 10-mg atogepant (95% confidence interval [CI], −1.8 to −0.6), −1.4 days with 30-mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60-mg atogepant (95% CI, −2.3 to −1.2) (P< 0.001 for all comparisons with placebo). Results for the secondary end points favored atogepant over placebo with the exceptions of the AIM-D Performance of Daily Activities score and the AIM-D Physical Impairment score for the 10-mg dose. The most common adverse

					events were constipation (6.9 to 7.7% across atogepant doses) and nausea (4.4 to 6.1% across atogepant doses). Serious adverse events included one case each of asthma and optic neuritis in the 10-mg atogepant group. Oral atogepant once daily was effective in reducing the number of migraine days and headache days over a period of 12 weeks. Adverse events included constipation and nausea. Longer and larger trials are needed to determine the effect and safety of atogepant for

					migraine prevention.
4	Patricia Pozo-Rosich et al.	Atogepant for the preventive treatment of chronic migraine **(PROGRESS)** : a randomized, double-blind, placebo-controlled, phase 3 trial[4]	To evaluate the impact of atogepant on key secondary and exploratory patient-reported outcomes (PROs) for measures of daily functioning and work productivity among individuals with chronic migraine (CM).	Changes from baseline in mean monthly Performance of Daily Activities (PDA) and Physical Impairment (PI) domain scores of the Activity Impairment in Migraine–Diary (AIM-D) across the 12-week treatment period. Key secondary endpoints: Changes from baseline in monthly PDA and PI domain scores of the AIM-D at weeks 1–4, 5–8, and 9–12 were exploratory endpoints Changes from baseline in absenteeism, presenteeism, overall work activity loss, and activity impairment domain scores of the Work Productivity and Activity	Both doses of atogepant demonstrated statistically significant improvements from baseline in mean monthly AIM-D PDA and PI domain scores across the 12-week treatment period vs placebo. Both atogepant doses demonstrated nominally significant improvements in AIM-D PDA and PI domain scores at weeks 1–4, 5–8, and 9–12 (only for 30 mg BID) vs placebo. Nominally significant improvements were seen in presenteeism, overall work productivity loss, and activity

				Impairment Questionnaire (WPAI): Migraine (WPAI) at weeks 4, 8, and 12 were exploratory endpoints	impairment for both atogepant doses at all time points, and in absenteeism at weeks 4 and 12 for both doses, vs placebo (nominal P<0.05). Atogepant demonstrated statistically significant improvements in PRO measures of migraine impact on daily functioning and work productivity in this CM study.

Conclusion Statement – Atogepant

Atogepant is a calcitonin gene-related peptide receptor antagonist. It is not registered by SFDA. Based on the clinical trials, atogepant demonstrates favorable outcomes. However, a notable limitation was that it was only compared to a placebo, and currently, there are no specific guidelines recommending its use as a line of therapy. On the other hand, positive reimbursement decisions by HTA CADTH and HAS have been granted based on specific conditions. The clinical approval for atogepant in 60mg/10mg doses has been obtained from SFDA, but the final step, pricing approval, is underway. Therefore, it is highly seen that Atogepant ranks at the forefront of the gepant family; however, the final judgment awaits the unveiling of its price.

Section 3.0 Key Recommendations Synthesis

Diagnoses of migraine can be refined based on the frequency of monthly migraine days and monthly headache days based on ICHD-3 criteria for migraine and chronic migraine.

Use of nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (e.g., aspirin + acetaminophen + caffeine) for mild-to- moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE], small-molecule CGRP receptor antagonists [gepants], selective serotonin (5-HT1F) receptor agonist [ditan]) for moderate or severe attacks and mild-to moderate attacks that respond poorly to nonspecific therapy is recommended.

For acute treatment of Migraine with or without Aura: people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated: Consider a non-oral preparation of metoclopramide or prochlorperazine and If non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID or triptan if they have not been tried.

In individuals with episodic migraine: eptinezumab, erenumab, fremanezumab and galcanezumab are recommended as preventive treatment (strong recommendation).

In individuals with chronic migraine: eptinezumab, erenumab, fremanezumab and galcanezumab are recommended as preventive treatment (strong recommendation).

In individuals with **episodic or chronic migraine**: erenumab is recommended over topiramate as preventive treatment (strong recommendation).

Several new drugs were approved by the FDA for treatment and for preventive treatment. No changes or modifications were made to existing drugs. However, it is worth noting that three drugs previously used in Saudi Arabia, are no longer registered with the SFDA: Amitriptyline, Nortriptyline and Tolfenamic acid.

For Erenumab: a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults. HTA recommendations for Erenumab were mostly favorable for the reimbursement of the medication, yet criteria for inclusion were set by CADTH, NICE and HAS. At the same time, all HTAs recommended a price reduction or partial reimbursement. Based on the above, we suggest considering adding Erenumab for prevention of migraine for patients who have 4 or more migraine days a month and at least 3 preventive drug treatments have failed with prior authorization and conditional approval considering the inclusion criteria as set by HTAs Assessment.

For Galcanezumab: a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults). The clinical benefit

according to HAS evaluation was substantial in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease. Similar recommendations were identified by NICE and IQWIG. Yet, CADTH opinion was not favoring reimbursement Emgality® of versus other effective therapies based on cost effectiveness concerns. Based on the above, we suggest considering adding Emgality® for prevention of migraine with prior authorization and conditional approval for patients who have 4 or more migraine days a month and at least 3 preventive drug treatments have failed.

For Ubrogepant: the first Ubrogepant, the first drug in the gepant class to receive FDA approval for the acute treatment of migraine but didn't get the approval for prevention of Migraine episodes. It was approved by the Saudi FDA and US FDA only. Based on the HTA evaluation of CADTH in 2023, there is no positive recommendation to include this medication for the treatment of Migraine.

For Lasmiditan: the first drug in the ditan class to receive FDA approval for the acute treatment of migraine but didn't get the approval for prevention of Migraine episodes. It was approved by the Saudi FDA, EMA, and US FDA. • Lasmiditan is also associated with euphoria and hallucinations, suggesting abuse potential. The controlled substance schedule for Lasmiditan is under review by the US Drug Enforcement Administration. It can be approved for use of migraine with prior authorization awaiting the classification by the US drug enforcement administration.

New drugs not registered by SFDA: According to the Canadian Agency for Drugs and Technologies in Health (CADTH) which is the only organization who evaluated Rimegepant, there are concerns about the use of Rimegepant in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases. Zavegepant is a calcitonin gene-related peptide receptor antagonist given via intranasal route. It is not registered by SFDA, nor evaluated by HTA agencies. As a result, we do not suggest the inclusion of Zavegepant nor Rimegepant especially that both are not SFDA approved yet.

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Migraine report** and aims to provide recommendations to aid in the management of Migraine. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Migraine. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Goadsby PJ, Evers S. International Classification of Headache Disorders - ICHD-4 alpha. *Cephalalgia*. 2020;40(9):887-888. doi:10.1177/0333102420919098
2. Mínguez-Olaondo A, Quintas S, Morollón Sánchez-Mateos N, et al. Cutaneous Allodynia in Migraine: A Narrative Review. *Front Neurol*. 2021;12. doi:10.3389/FNEUR.2021.831035
3. Kalita J, Yadav RK, Misra UK. A comparison of migraine patients with and without allodynic symptoms. *Clin J Pain*. 2009;25(8):696-698. doi:10.1097/AJP.0B013E3181B12DD3
4. Benatto MT, Florencio LL, Carvalho GF, et al. Cutaneous allodynia is more frequent in chronic migraine, and its presence and severity seems to be more associated with the duration of the disease. *Arq Neuropsiquiatr*. 2017;75(3):153-159. doi:10.1590/0004-282X20170015
5. Güven H, Çilliler AE, Çomoğlu SS. Cutaneous allodynia in patients with episodic migraine. *Neurol Sci*. 2013;34(8):1397-1402. doi:10.1007/S10072-012-1249-9
6. Buse DC, Scher AI, Dodick DW, et al. Impact of Migraine on the Family: Perspectives of People with Migraine and Their Spouse/Domestic Partner in the CaMEO Study. *Mayo Clin Proc*. 2016;91(5):596-611. doi:10.1016/j.mayocp.2016.02.013
7. Understanding the American Migraine Prevalence and Prevention Study. Accessed July 1, 2023. https://americanmigrainefoundation.org/resource-library/ampp/
8. Serrano D, Manack AN, Reed ML, Buse DC, Varon SF, Lipton RB. Cost and predictors of lost productive time in chronic migraine and episodic migraine: Results from the American Migraine Prevalence and Prevention (AMPP) Study. *Value in Health*. 2013;16(1):31-38. doi:10.1016/J.JVAL.2012.08.2212
9. Feigin VL, Krishnamurthi R V., Theadom AM, et al. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16(11):877-897. doi:10.1016/S1474-4422(17)30299-5
10. Global Health Estimates. Accessed July 1, 2023. https://www.who.int/data/global-health-estimates
11. Munakata J, Hazard E, Serrano D, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2009;49(4):498-508. doi:10.1111/J.1526-4610.2009.01369.X

12. Raval AD, Shah A. National Trends in Direct Health Care Expenditures Among US Adults With Migraine: 2004 to 2013. *J Pain*. 2017;18(1):96-107. doi:10.1016/J.JPAIN.2016.10.005

13. Rajeh S Al, Awada A, Bademosi O, Ogunniyi A. The prevalence of migraine and tension headache in Saudi Arabia: a community-based study. *Eur J Neurol*. 1997;4(5):502-506. doi:10.1111/J.1468-1331.1997.TB00391.X

14. Al Jumah M, Al Khathaami AM, Kojan S, Hussain M, Thomas H, Steiner TJ. The prevalence of primary headache disorders in Saudi Arabia: a cross-sectional population-based study. *J Headache Pain*. 2020;21(1). doi:10.1186/S10194-020-1081-1

15. Abu-Salameh I, Plakht Y, Ifergane G. Migraine exacerbation during Ramadan fasting. *J Headache Pain*. 2010;11(6):513-517. doi:10.1007/S10194-010-0242-Z

16. Andress-Rothrock D, King W, Rothrock J. An Analysis of Migraine Triggers in a Clinic-Based Population. *Headache: The Journal of Head and Face Pain*. 2010;50(8):1366-1370. doi:10.1111/J.1526-4610.2010.01753.X

17. Burch R. Migraine and Tension-Type Headache Diagnosis and Treatment. doi:10.1016/j.mcna.2018.10.003

18. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology*. 2015;84(7):688-695. doi:10.1212/WNL.0000000000001256

19. Ailani J, Burch RC, Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache: The Journal of Head and Face Pain*. 2021;61(7):1021-1039. doi:10.1111/HEAD.14153

20. Headaches in over 12s: diagnosis and management. *Headaches in over 12s: diagnosis and management*. Published online December 17, 2021. Accessed June 29, 2023. https://www.ncbi.nlm.nih.gov/books/NBK553317/

21. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *Journal of Headache and Pain*. 2019;20(1):1-33. doi:10.1186/S10194-018-0955-Y/TABLES/20

22. Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review - GOV.UK. Accessed June 30, 2023. https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review#national-review-of-safety-data

23. (3) (PDF) Clinical Practice Guideline on Migraine Headache Diagnosis & Management: Kingdom of Saudi Arabia EBHC. Accessed June 30, 2023.

https://www.researchgate.net/publication/294425019_Clinical_Practice_Guideline_on_Migraine_Headache_Diagnosis_Management_Kingdom_of_Saudi_Arabia_EBHC

24. Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine : a national clinical guideline. :45. Accessed October 3, 2023. https://testing36.scot.nhs.uk

25. Pellesi L, De Icco R, Alawie HY, et al. A systematic review, meta-analysis and meta-regression evaluating the adverse reactions to erenumab in the preventive treatment of migraine. *Expert Opin Drug Saf*. 2021;20(4):467-474. doi:10.1080/14740338.2021.1866537

26. Service Line: CADTH Drug Reimbursement Recommendation Version: 1.0. Published online 2020.

27. Overview | Erenumab for preventing migraine | Guidance | NICE. Accessed June 23, 2023. https://www.nice.org.uk/guidance/ta682

28. Haute Autorité de Santé - AIMOVIG (erenumab). Accessed June 30, 2023. https://www.has-sante.fr/jcms/c_2908652/fr/aimovig-erenumab

29. [A18-71] Erenumab (prophylaxis of migraine) - Benefit assessment according to §35a Social Code Book V. Accessed June 30, 2023. https://www.iqwig.de/en/projects/a18-71.html

30. galcanezumab | CADTH. Accessed June 23, 2023. https://www.cadth.ca/galcanezumab

31. 1 Recommendations | Galcanezumab for preventing migraine | Guidance | NICE. Accessed June 23, 2023. https://www.nice.org.uk/guidance/TA659/chapter/1-Recommendations

32. Haute Autorité de Santé - EMGALITY. Accessed June 23, 2023. https://www.has-sante.fr/jcms/p_3191463/en/emgality

33. [A19-63] Galcanezumab (migraine) - Addendum to commission A19-28. Accessed June 23, 2023. https://www.iqwig.de/en/projects/a19-63.html

34. Small Molecule Calcitonin Gene-Related Peptide Receptor Antagonists for the Acute Treatment of Migraine | CADTH. Accessed June 23, 2023. https://www.cadth.ca/small-molecule-calcitonin-gene-related-peptide-receptor-antagonists-acute-treatment-migraine

35. Overview | Rimegepant for preventing migraine | Guidance | NICE.

36. Pratt B, Fitzgerald D. CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 211280Orig1s000 RISK ASSESSMENT AND RISK MITIGATION REVIEW(S) 1 Division of Risk Management (DRISK) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) Center for Drug Evaluation and Research (CDER) Application Type NDA Application Number 211280

PDUFA Goal Date Subject Evaluation of need for a REMS. Published online 2019.

37. Controlled Substance Schedules. Accessed October 13, 2023. https://www.deadiversion.usdoj.gov/schedules/

38. Federal Register :: Schedules of Controlled Substances: Placement of Lasmiditan in Schedule V. Accessed October 13, 2023. https://www.federalregister.gov/documents/2021/05/24/2021-10827/schedules-of-controlled-substances-placement-of-lasmiditan-in-schedule-v

39. Clair JS. A New Model of Tracheostomy Care: Closing the Research–Practice Gap. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 3: Implementation Issues). Rockville (MD): Agency fo.

Section 6.0 Appendices

Appendix A. Prescribing Edits

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.
Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

I. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

II. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

III. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

IV. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

V. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Adopted

Grade of research[39]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. Migraine Prevention Algorithm

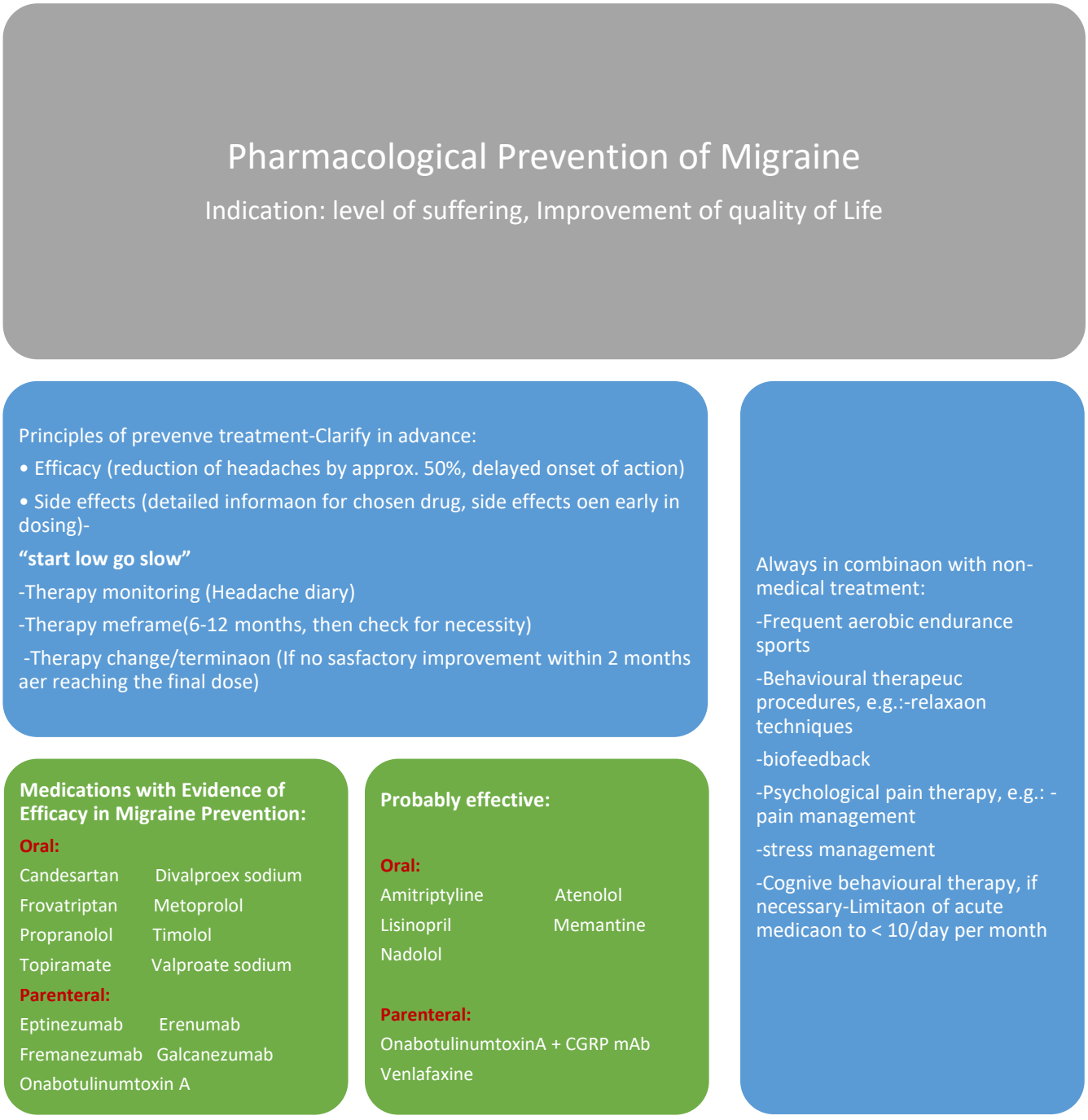

Figure 1. *Treatment Algorithm for the Prevention of Migraine*

Appendix D. PubMed search

The following is the result of the PubMed search conducted for Migraine guideline search:

Query	Filters	Search Details	Results
migraine headache	Guideline, in the last 5 years	("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR ("migraine"[All Fields] AND "headache"[All Fields]) OR "migraine headache"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	18
migraine guidelines	Guideline, in the last 5 years	(("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	20
american headache society	Guideline, in the last 5 years	(("american"[All Fields] OR "american s"[All Fields] OR "americanization"[All Fields] OR "americanized"[All Fields] OR "americans"[All Fields]) AND ("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields]) AND ("societies"[MeSH Terms] OR "societies"[All Fields] OR "society"[All Fields] OR "society s"[All Fields] OR "societys"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	10
european headache federation	Guideline, in the last 5 years	(("european people"[MeSH Terms] OR ("european"[All Fields] AND "people"[All Fields]) OR "european people"[All Fields] OR "european"[All Fields] OR "europeans"[All Fields]) AND ("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields]) AND	6

		("federal"[All Fields] OR "federalism"[All Fields] OR "federalization"[All Fields] OR "federalized"[All Fields] OR "federalizing"[All Fields] OR "federally"[All Fields] OR "federate"[All Fields] OR "federated"[All Fields] OR "federates"[All Fields] OR "federating"[All Fields] OR "federation"[All Fields] OR "federation s"[All Fields] OR "federations"[All Fields] OR "federative"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	
(American Academy of Neurology) AND (Migraine)	Guideline, in the last 5 years	(("american"[All Fields] OR "american s"[All Fields] OR "americanization"[All Fields] OR "americanized"[All Fields] OR "americans"[All Fields]) AND ("academie"[All Fields] OR "academies and institutes"[MeSH Terms] OR ("academies"[All Fields] AND "institutes"[All Fields]) OR "academies and institutes"[All Fields] OR "academies"[All Fields] OR "academy"[All Fields] OR "academy s"[All Fields]) AND ("neurology"[MeSH Terms] OR "neurology"[All Fields] OR "neurology s"[All Fields]) AND ("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	4
(American Academy of Neurology and the American Headache Society) AND (Migraine)	Guideline, in the last 5 years	(("american"[All Fields] OR "american s"[All Fields] OR "americanization"[All Fields] OR "americanized"[All Fields] OR "americans"[All Fields]) AND ("academie"[All Fields] OR	3

		"academies and institutes"[MeSH Terms] OR ("academies"[All Fields] AND "institutes"[All Fields]) OR "academies and institutes"[All Fields] OR "academies"[All Fields] OR "academy"[All Fields] OR "academy s"[All Fields]) AND ("neurology"[MeSH Terms] OR "neurology"[All Fields] OR "neurology s"[All Fields]) AND ("american"[All Fields] OR "american s"[All Fields] OR "americanization"[All Fields] OR "americanized"[All Fields] OR "americans"[All Fields]) AND ("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields]) AND ("societies"[MeSH Terms] OR "societies"[All Fields] OR "society"[All Fields] OR "society s"[All Fields] OR "societys"[All Fields]) AND ("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	

((migraine)) AND (headache)	**Guideline, in the last 5 years**	**(("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))**	**14**
((migraine)) AND (headache)	in the last 5 years	(("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields])) AND (y_5[Filter])	6,794

Appendix E. Scope

2020 Version	Changes Performed	2023 (Current version)	Rationale/Description
Not available	New section	Scope	Summarize the main changes and updates between the 2020 and 2023 versions
Executive Summary	**Updated**	Background	A general overview covering pathophysiological and epidemiological aspects was added.
Section 1. MIGRAINE CLINICAL GUIDELINES			
NICE guidelines 2012, updated 2015	**Updated**	Headaches in over 12s: diagnosis and management; Clinical guideline. Published: 19 September 2012 Last updated: 17 December 2021	Main updates: In May 2021, they amended their recommendation on topiramate for migraine prophylaxis, relaying on MHRA advice, to include discussion of the potential benefits and risks, and the importance of effective contraception for women and girls of childbearing potential when taking topiramate. In December 2021, the strength of the recommendation on metoclopramide or prochlorperazine for acute migraine was changes from 'offer' to 'consider', to better reflect the balance of benefits and risks of these treatments.
Evidence-based guideline update: Pharmacologic treatment for	**Updated**	The American Headache Society Consensus Statement: Update on integrating new migraine	This update, which is based on the expanded evidence base and emerging expert consensus concerning post approval usage,

episodic migraine prevention in adults [2012] Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society		treatments into clinical practice, 2021	provides practical recommendations in the absence of a formal guideline. Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.
Not available	New section	Migraine Headache: Diagnosis & Management, KSA 2015	the Ministry of Health of the Kingdom of Saudi Arabia with the support of the McMaster University Working Group produced practice guidelines to assist health care providers in evidence-based decision-making on the diagnosis and management of migraine headache.
Section 2. DRUG THERAPY FOR MIGRAINE			
calcitonin gene-related peptide receptor antagonist	Addition of a medication	Zavzpret® (zavegepant) Pfizer	FDA Approved in March 2023 for the acute treatment of migraine with or without aura in adults. Not registered by SFDA
calcitonin gene-related peptide receptor antagonist	Addition of a medication	Nurtek ODT ® (Rimegepant) Biohaven Pharma	FDA Approved in 2020 for the acute treatment of migraine with or without aura in adults. Not registered by SFDA

			NICE: HTA recommendation for prevention of Migraine will be published in 5 July 2023 and the one for treatment of migraine will be published in October 2023. CADTH: Two gepants, rimegepant and ubrogepant, have completed phase III trials for the acute treatment of migraine. • No studies comparing the gepants to other acute treatment of migraine were identified and thus their relative efficacy and safety to the triptans and their place in therapy are unknown. The studies evaluated the gepants on a single episode of a migraine attack which did not permit the assessment of the consistency of the effects of the drugs over time • Although the cost of the drugs in Canada is not available, it is likely to have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers. • Clinical trials on rimegepant excluded patients with current evidence of uncontrolled, unstable or recently diagnosed

			cardiovascular disease. This raises concerns about the use of these drug in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases. Further, clinical trials on rimegepant also excluded patients with current diagnosis of major depression, a condition that is commonly comorbid with migraine
calcitonin gene-related peptide receptor antagonist	Addition of a medication	Ubrelvy® (Ubrogepant)	FDA approved in 2019 for the acute treatment of migraine with or without aura in adults. Ubrelvy is not indicated for the preventive treatment of migraine. Registered by SFDA, nut not listed by CHI CADTH 2023: • No studies comparing the gepants to other acute treatment of migraine were identified and thus their relative efficacy and safety to the triptans and their place in therapy are unknown. The studies evaluated the gepants on a single episode of a

			migraine attack which did not permit the assessment of the consistency of the effects of the drugs over time • Although the cost of the drugs in Canada is not available, it is likely to have a significant budget impact due to the high prevalence of migraine and the unmet need of migraine treatments in up to one-third of migraine sufferers. • Clinical trials on ubrogepant excluded patients with clinically significant cardiovascular diseases. This raises concerns about the use of these drug in patients with cardiovascular diseases which is an unmet need in migraine therapy, as triptans are contraindicated in patients with cardiovascular diseases.
serotonin (5-HT) 1F receptor agonis	Addition of a medication	Reyvow® (lasmiditan)	FDA approved in 2019 for the acute treatment of migraine with or without aura in adults. It is not indicated for the preventive treatment of migraine. Registered by SFDA, nut not listed by CHI
serotonin (5-HT) 1B/1D receptor agonis	Addition of a medication	RIZAFILM® (Rizatriptan)	FDA approved in 2023 as oral film for treatment of acute migraine.

			The oral film is not registered by SFDA
Calcitonin gene-related peptide receptor antagonist	Addition of a medication	Aimovig® Erenumab-aooe	FDA approved in 2018 for the preventive treatment of migraine in adults. Registered by SFDA but not listed by CHI HAS 2022: Favourable opinion for reimbursement only in patients with severe migraine and at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina or coronary artery bypass graft (CABG)). Clinical benefit now substantial (previously it was moderate) in this indication considering the following elements: • severity of the disease and its prevalence, • the partially covered medical need in severe migraine situations (≥ 8 migraine days per month) after previous failure to at least two prophylactic treatments, with the need to have access to more effective prophylactic treatments with fewer adverse effects,

			• the lack of additional response to the identified need, with the absence of an additional impact on morbidity in severe migraine situations after failure to at least two prophylactic treatments, and the absence of new data in terms of the impact on quality of life in this chronic, incapacitating condition, • the absence of data relative to an additional impact on the care pathway of patients • AIMOVIG (erenumab) is unlikely to have an additional impact on public health. Considering all these elements, the Committee deems that the clinical benefit of AIMOVIG (erenumab) is high in patients with severe migraine and at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina or coronary artery bypass graft (CABG)). The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products

			approved for use in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, stroke, TIA, unstable angina or coronary artery bypass graft (CABG)). Recommended reimbursement rate: 65% IQWIG 2019: Erenumab was approved for both episodic and chronic migraine. The study results evaluated also do not have to be restricted to episodic migraine as the literature provides no medical or other substantive justification for the value of "14 days" to distinguish episodic from chronic migraine. In addition, the participants in the LIBERTY study were in the transition period between episodic and chronic migraine. Overall, IQWiG therefore sees an indication of a considerable added benefit of erenumab for the prophylaxis of migraine. NICE 2023: The cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources. So

			erenumab is recommended for preventing migraine in adults who have at least 4 migraine days per month. Erenumab is recommended as an option for preventing migraine in adults, only if: • they have 4 or more migraine days a month • at least 3 preventive drug treatments have failed • the 140 mg dose of Erenumab is used and • the company provides it according to the commercial arrangement. Nice also recommended to Stop Erenumab after 12 weeks of treatment if: • in episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50% • In chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%. To note that these recommendations are not intended to affect treatment with Erenumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without

			change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. CADTH 2020: The Canadian Drug Expert Committee recommends that erenumab be reimbursed for the prevention of chronic migraine in adults, if the following conditions are met. Initiation criteria: 1. The patient has a confirmed diagnosis of chronic migraine according to the International Headache Society criteria, which defined it as headaches that last for at least 15 days per month for more than three months of which at least eight days per month are with migraine. 2. The patient has experienced an inadequate response, intolerance, or contraindication to two or three oral prophylactic migraine medications. 3. Patients who have had a lack of therapeutic response to four or more prior oral prophylactic migraine medications are not

			eligible for reimbursement. 4. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement. 5. The maximum duration of initial authorization is six months. As for the renewal criteria: 1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the number of migraine days per month has been maintained. 2. The maximum duration of subsequent authorizations following the initial authorization is six months. As a prescribing conditions: The patient should be under the care of a physician who has the appropriate qualifications and experience with the

			management of migraine headaches. CADTH also recommended that price must be reduced.
calcitonin gene-related peptide antagonist	Addition of a medication	Emgality® (galcanezumab-gnlm)	FDA approved in 2018 for preventive treatment of migraine in adults. Registered by SFDA HAS 2020: Favourable opinion for reimbursement in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis (DVT) or other serious cardiovascular risk). • The clinical benefit of EMGALITY (galcanezumab) is **substantial** in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass

			graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis (DVT) or other serious cardiovascular risk). Unfavourable opinion for reimbursement in the rest of the MA indication: The clinical benefit of EMGALITY (galcanezumab) is insufficient to justify its funding by the French national health insurance system in other patients falling within the scope of the MA indication. Also considering the availability of short-term safety data (maximum follow-up of 1 year) with uncertainties with respect to long-term safety, in particular in terms of cardiological and immunogenicity risks, the Committee considers that EMGALITY (galcanezumab) **provides no clinical added value (CAV V)** in adult patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis

			(DVT) or other serious cardiovascular risk). NICE 2020: For episodic and chronic migraine, the most likely cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So galcanezumab is recommended for episodic and chronic migraine. Galcanezumab is recommended as an option for preventing migraine in adults, only if: • they have 4 or more migraine days a month • at least 3 preventive drug treatments have failed and • the company provides it according to the commercial arrangement. Stop galcanezumab after 12 weeks of treatment if: • in episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50% • in chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%. This recommendation is not intended to affect treatment with galcanezumab that was

			started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. CADTH: CADTH recommends that Emgality should be reimbursed by public drug plans for the prevention of migraine if certain conditions are met. It should only be covered to prevent migraine attacks in adult patients who have tried at least 2 other types of oral preventive medications. Emgality should only be reimbursed if the patient is being cared for by a physician who has experience managing migraine headaches. Emgality will only be reimbursed for 6 months at a time. Emgality should not be more than the least costly drug of the same class used to prevent migraine. Recommendation is based on Evidence from 4 clinical trials that demonstrated that Emgality reduced the frequency of migraine headache days, and migraine-related disability. Emgality may also reduce

			migraine intensity, the use of acute pain medication, and improve daily functioning and health-related quality of life. • There is no evidence to suggest Emgality is more effective than other reimbursed therapies used to treat patients with migraines. Therefore, Emgality should be priced no more than the lowest cost alternative to ensure cost-effectiveness. • Economic evidence suggests the price of Emgality must be reduced by approximately 49% to 78% to ensure Emgality is cost-effective at a $50,000 per quality-adjusted life-year (QALY) threshold. IQWIG 2019: there is an indication of major added benefit of galcanezumab versus BSC for adult patients who have at least 4 migraine days/month and for whom best supportive care (BSC) is the only treatment option: Patients who do not respond to any of the following treatments (drug classes), are unsuitable for them or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, clostridium botulinum toxin type A.

Not existing	**New section**	**Section 4. Key Recommendations Synthesis**	
Not existing	**New section**	**Section 5. Conclusion**	
References	Updated	**Section 6. References**	
Appendices	Updated	**Section 7. Appendices**	