Medicines Management Programme

Managed Access Protocol – Calcitonin gene-related peptide (CGRP) monoclonal antibodies (MABs) for the prophylaxis of chronic migraine in adults:

eptinezumab (Vyepti®)▼

erenumab (Aimovig®)

fremanezumab (Ajovy®)▼

galcanezumab (Emgality®)▼

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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List of Abbreviations

CGRP	Calcitonin gene-related peptide
HSE	Health Service Executive
HTH	High Tech Hub
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
IV	Intravenous
MAB	Monoclonal antibody
MAP	Managed Access Protocol
MMD	Monthly migraine days
MMP	Medicines Management Programme
PCRS	Primary Care Reimbursement Service
PFP	Pre-filled pen
PFS	Pre-filled syringe
SC	Subcutaneous
SmPC	Summary of Product Characteristics

1. Calcitonin gene-related peptide monoclonal antibodies

There are three calcitonin gene-related peptide (CGRP) monoclonal antibodies (MABs) available under the High Tech Arrangement and one CGRP MAB available under hospital pricing approval.

CGRP MABs available under the High Tech Arrangement:

- Erenumab: Aimovig® solution for injection in pre-filled pen (PFP) 70 mg or 140 mg
- Fremanezumab: Ajovy® solution for injection in pre-filled syringe (PFS) 225 mg▼[i] and Ajovy® solution for injection in pre-filled pen (PFP) 225 mg▼[i]
- Galcanezumab: Emgality® solution for injection in pre-filled pen (PFP) 120 mg▼[i].

CGRP MAB available under hospital pricing approval:

- Eptinezumab: Vyepti® 100 mg concentrate for solution for infusion▼[i].

This Managed Access Protocol (MAP) outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of erenumab, fremanezumab or galcanezumab under the High Tech Arrangement, or eptinezumab under hospital pricing approval.

1.1 Licensed indication

Eptinezumab (Vyepti®), erenumab (Aimovig®), fremanezumab (Ajovy®) and galcanezumab (Emgality®) are indicated for the prophylaxis of migraine in adults who have at least four migraine days per month.[ii]

1.2 Reimbursement

Conditional reimbursement of erenumab, fremanezumab and galcanezumab on the High Tech Arrangement, and eptinezumab under hospital pricing approval, is confined to the following subgroup of the licensed population:

- prophylaxis of chronic migraine in adults who have failed three or more prophylactic treatments.

Prescribers are required to apply for reimbursement approval on an individual patient basis through the online application system.

[i] ▼This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions

[ii] Please refer to each individual product's Summary of Product Characteristics for full prescribing information

1.2.1 High Tech Arrangement

If a patient is recommended for reimbursement of a CGRP MAB, and the prescriber wishes to prescribe erenumab (Aimovig®), fremanezumab (Ajovy®) or galcanezumab (Emgality®), the High Tech prescription for the required CGRP MAB should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated for erenumab (Aimovig®), fremanezumab (Ajovy®) or galcanezumab (Emgality®) will not be eligible for reimbursement by the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS).

If a patient is recommended for reimbursement of a CGRP MAB, reimbursement of erenumab, fremanezumab and galcanezumab will be supported in line with the licensed therapeutic dosage.

- **Erenumab**: reimbursement will be supported for a maximum of 13 Aimovig® 70 mg or 140 mg PFP per year, i.e. the patient should be prescribed a dose of 70 mg or 140 mg of erenumab by subcutaneous (SC) injection every four weeks.
- **Fremanezumab**: reimbursement will be supported for a maximum of 12 Ajovy® 225 mg PFS/ Ajovy® 225 mg PFP per year, i.e. the patient should be prescribed a dose of fremanezumab 225 mg once monthly or 675 mg once every three months by SC injection.
- **Galcanezumab:** reimbursement will be supported for a maximum of two Emgality® 120 mg PFP for the loading dose (first month of treatment) and one Emgality® 120 mg PFP once monthly thereafter, i.e. the patient should be prescribed a dose of galcanezumab 120 mg once monthly (with a 240 mg loading dose as the initial dose) by SC injection.

1.2.2 Hospital pricing approval

Reimbursement of eptinezumab (Vyepti®) under hospital pricing approval is available for patients who are approved for reimbursement of a CGRP MAB following an application by an approved prescriber through the online application system.

If a patient is recommended for reimbursement of a CGRP MAB, reimbursement of eptinezumab will be supported in line with the licensed therapeutic dosage, i.e. 100 mg (one Vyepti® 100 mg vial) by intravenous (IV) infusion every 12 weeks; some patients may benefit from a dosage of 300 mg (three Vyepti® 100 mg vials) administered by IV infusion every 12 weeks.

Reimbursement of dosages in excess of the licensed therapeutic dosages for eptinezumab, erenumab, fremanezumab and galcanezumab is not supported. Reimbursement is not supported for concomitant use of CGRP MABs.

1.3 Reimbursement price

The reimbursement prices of one pack of erenumab (Aimovig®), fremanezumab (Ajovy®) and galcanezumab (Emgality®) available on the High Tech Arrangement as of 1 July 2023 are outlined in Table 1.

Table 1: Reimbursement prices of CGRP MABs available on the High Tech Arrangement

CGRP MAB	Medicinal product (pack size)	Reimbursement code	Reimbursement price
Erenumab	Aimovig® 70 mg PFP (one pen)	89090	€444.81
	Aimovig® 140 mg PFP (one pen)	89091	€445.50
Fremanezumab	Ajovy® 225 mg PFS (one syringe)	89094	€432.00
	Ajovy® 225 mg PFP (one pen)	89109	€432.00
Galcanezumab	Emgality® 120 mg PFP (one pen)	89169	€414.03

mg: milligrams; PFP: pre-filled pen; PFS: pre-filled syringe

The price to wholesaler of the presentation of eptinezumab (Vyepti®) available under hospital pricing approval as of 28 June 2023 is outlined in Table 2.

Table 2: Price to wholesaler of CGRP MAB available under hospital pricing approval

CGRP MAB	Medicinal product (pack size)	Price to wholesaler
Eptinezumab	Vyepti® 100 mg concentrate for solution for infusion (1 ml vial x 1)	€ 1,296.00

mg: milligrams; ml: millilitre

A commercial-in-confidence arrangement is in place with the marketing authorisation holders to reduce the net acquisition cost of Aimovig®, Ajovy®, Emgality® and Vyepti® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of eptinezumab, erenumab, fremanezumab and galcanezumab for prophylaxis of chronic migraine under the High Tech Arrangement/hospital pricing approval.

2.1 Prescribers

The prescribing of erenumab (Aimovig®), fremanezumab (Ajovy®) and galcanezumab (Emgality®) under the High Tech Arrangement and eptinezumab (Vyepti®) under hospital pricing approval will be confined to consultant neurologists registered with the Irish Medical Council, who have agreed to the

terms of this MAP and have been approved by the HSE. Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient clinical history

In line with the exclusion criteria for the pivotal licensing trials and information contained within the relevant Summary of Product Characteristics (SmPC), reimbursement of eptinezumab, erenumab, fremanezumab and galcanezumab will not be considered in the following patients:[iii]

- patients who are pregnant
- patients who are breast-feeding
- patients older than 50 years at migraine onset where alternative causes of headache have not been excluded
- patients with a recent history of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events.

Clinicians should consider persistent medication overuse, in particular with codeine containing analgesics or other opioid analgesics, as a relative contraindication to prescribing a CGRP MAB.

2.3 Patient age

Applications for reimbursement approval will only be considered for individuals aged 18 years and older at time of application. There is limited safety and efficacy data available on the use of CGRP MABs in patients aged 65 years and older.

2.4 Confirmed diagnosis of chronic migraine

The International Headache Society (IHS) defines chronic migraine as the occurrence of headache on 15 or more days per month for more than three months, which on at least eight days per month, has the features of migraine headache.

Clinicians will be required to confirm the diagnosis of chronic migraine at the time of application. The diagnosis of chronic migraine should be made in line with the 3rd edition of the International Classification of Headache Disorders (ICHD-3) diagnostic criteria, as outlined in Appendix 1.

[iii] This list is not exhaustive; please refer to each individual product's Summary of Product Characteristics for full prescribing information.

2.4.1 Number of monthly migraine days

Clinicians will be required to confirm the number of migraine days the patient experiences in the four-week period prior to the date of application, i.e. baseline monthly migraine days (MMD)**.** Prophylactic treatment(s) the patient received during this four-week period should be outlined.

- ***A migraine day*** *is defined as any calendar day on which the patient has an onset, continuation, or recurrence of a qualified migraine.*
- ***A qualified migraine*** *is defined as a migraine headache (with or without aura) lasting for at least four hours continuously, with reports of either two or more pain features (unilateral, throbbing, moderate-to-severe intensity, or aggravation by exercise or physical activity) or one or more associated non-pain features (nausea or vomiting, or both photophobia and phonophobia). If a patient takes an acute migraine-specific drug during aura or to treat a headache during a calendar day, the day should be counted as a migraine day regardless of the headache duration and pain features or associated symptoms.*

2.5 Previous prophylactic treatments

Evidence of treatment failure with at least three prophylactic treatments outlined in table 3 must be included in the application for reimbursement approval.

Treatment failure for oral prophylactic treatments is defined as:

- an inadequate response after confirmed adherence to treatment for a period of at least three consecutive months at the maximum tolerated dose, or
- discontinuation of treatment due to a clinically significant adverse reaction prior to completion of a period of at least three consecutive months at the maximum tolerated dose.

Table 3: Prophylactic treatments for which treatment failure with three must be demonstrated prior to an application for reimbursement approval of CGRP MABs under the High Tech Arrangement/ hospital pricing approval

Prophylactic treatment	
Oral	Acetazolamide
	Amitriptyline/ Dosulepin/ Nortriptyline
	Atenolol/ Metoprolol/ Propranolol
	Candesartan
	Flunarizine
	Pizotifen
	Sodium valproate
	Topiramate
	Venlafaxine
Intramuscular	Botulinum Toxin Type A (Botox®)
Intravenous	Dihydroergotamine

Not all treatments in table 3 are licensed for the prophylaxis of migraine. Please refer to individual SmPCs for further information. In the case of Botulinum Toxin Type A (Botox®), an adequate trial is considered to be two cycles of Botox® injections administered 12 weeks apart.

In cases where a patient experienced a clinically significant adverse reaction to a prophylactic treatment in table 3 which led to discontinuation of treatment prior to completion of a period of at least three consecutive months at the maximum tolerated dose, information in relation to the duration of treatment and the adverse reaction experienced should be provided in the application.

When reviewing applications, the HSE-Medicines Management Programme (MMP) may request additional evidence to demonstrate that the patient experienced treatment failure with prophylactic treatments.

3. Reimbursement criteria- Continuation

In chronic migraine, a 30% reduction in migraine frequency is considered a clinically meaningful response to treatment.

Ongoing reimbursement approval is conditional on a reduction of at least 30% in MMD following:

- three months of treatment with erenumab, fremanezumab or galcanezumab, or
- six months of treatment with eptinezumab.

This reduction in MMD should be sustained at future reviews and audits. Patients not showing this reduction in MMD after three months of treatment with erenumab, fremanezumab or galcanezumab, or after six months of treatment with eptinezumab, would be considered non-responders, or non-adherent to treatment. Reimbursement support may not continue for these patients.

Therefore following approval of a patient for reimbursement of erenumab, fremanezumab and galcanezumab under the High Tech Arrangement and eptinezumab under hospital pricing approval, the prescribing clinician is required to submit, upon request by the MMP, the following outcome data:

- MMD for a specific period i.e. number of migraine days for a four-consecutive week period as specified.

Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

4. Prescribing of CGRP MABs

Please refer to individual SmPCs for eptinezumab (Vyepi®), erenumab (Aimovig®), fremanezumab (Ajovy®) and galcanezumab (Emgality®) for full prescribing information including monitoring and patient counselling requirements. Only approved prescribers will have access to prescribe erenumab, fremanezumab and galcanezumab on the High Tech Arrangement and are eligible to prescribe eptinezumab under hospital pricing approval.

The following confirmations are required when prescribing eptinezumab, erenumab, fremanezumab and galcanezumab:

- Confirmation that eptinezumab (Vyepi®)/ erenumab (Aimovig®)/ fremanezumab (Ajovy®)/ galcanezumab (Emgality®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE
- Confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP

- Confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

**** Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.***

Appendix 1: ICHD-3 Chronic Migraine diagnostic criteria[iv]

A. Headache (migraine-like or tension-type-like) on ≥ 15 days per month for at least three months, and fulfilling criteria B and C.

B. Occurring in a patient who has had at least five migraine attacks fulfilling:

Migraine without aura:

- Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- 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)
- During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia **and/or**

Migraine with aura:

- One or more of the following fully reversible aura symptoms:
    1. visual
    2. sensory
    3. speech and/or language
    4. motor
    5. brainstem
    6. retinal
- At least three of the following six characteristics:
    1. at least one aura symptom spreads gradually over ≥5 minutes
    2. two or more aura symptoms occur in succession
    3. each individual aura symptom lasts 5 - 60 minutes
    4. at least one aura symptom is unilateral
    5. at least one aura symptom is positive
    6. the aura is accompanied, or followed within 60 minutes, by headache.

[iv] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38(1):1–211.

C. **On at least 8 days per month for at least 3 months, fulfilling any of the following**:

i. *Migraine without aura*

- 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)
- During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia

ii. *Migraine with aura*

- One or more of the following fully reversible aura symptoms:
    1. visual
    2. sensory
    3. speech and/or language
    4. motor
    5. brainstem
    6. retinal
- At least three of the following six characteristics:
    1. at least one aura symptom spreads gradually over ≥5 minutes
    2. two or more aura symptoms occur in succession
    3. each individual aura symptom lasts 5-60 minutes
    4. at least one aura symptom is unilateral
    5. at least one aura symptom is positive
    6. the aura is accompanied, or followed within 60 minutes, by headache

iii. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D. Not better accounted for by another ICHD-3 diagnosis.