NHS Kent and Medway

The use of Botulinum toxin type A and calcitonin gene-related peptide inhibitors for preventing migraine in adults

Version 1.7

Date: 9th August 2022

Approved by: July JPC Ratified by: Kate Langford MD
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Contact Details

Name	Geoffrey Howell Rebecca Aderinola
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Produced in consultation with:

Dr Andrew Dowson	Clinical Lead East Kent Headache Service, Bethesda Medical Centre
Dr Gerald Saldanha	Consultant Neurologist – Maidstone and Tunbridge Wells NHS Trust
Dr Ivona Tylova	Consultant Neurologist – Dartford and Gravesham NHS Trust

Change history

Version	Date	Comments
1.0	24th August 2020	Developed by Geoffrey Howell
1.1	2nd December 2020	Inclusion of Galcanezumab (Emgality®) following publication of NICE TA659
1.2	15th March 2021	Inclusion of Erenumab (Aimovig®) following publication of NICE TA682
1.3	19th March 2021	Minor amendments
1.4	24th March 2021	Amendments following discussion with Pharmaceutical Commissioning Team, NHS Surrey Heartlands CCG
1.5	2nd March 2022	Inclusion of Fremanezumab (Ajovy) in EM following publication of NICE TA764
1.6	29th June 2022	Adjustment to logo to state 'NHS Kent and Medway' and structure of EM diagram. Content remains the same as 1.5.
1.7	9th August 2022	Amendment to sections which refer to Botulinum neurotoxin as a HCD and all sections adjusted to reflect Botulinum neurotoxin is now within tariff.

NHS Kent and Medway CCG include four integrated care partnerships: Medway and Swale ICP, West Kent ICP, East Kent ICP and Dartford Gravesham and Swanley ICP. They are referred to collectively in this document forthwith as "Kent and Medway CCG" or the "Authority".

Contents

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Scope of pathway

The purpose of this clinical pathway is to provide clinicians with information on the prescribing of medication for adult patients presenting with migraine. The pathway only focuses on the prophylaxis of migraine with Botulinum toxin type A, Fremanezumab (Ajovy®), Galcanezumab (Emgality®) and Erenumab (Aimovig®). The recommendations for prescribing are based on NICE TA and the medications summary of product characteristics:

Botulinum toxin type A
NICE TA260: https://www.nice.org.uk/guidance/ta260/chapter/1-Guidance
SPC: https://www.medicines.org.uk/EMC/medicine/112/SPC/BOTOX+100+Units/

Fremanezumab (Ajovy®)
NICE TA764: https://www.nice.org.uk/guidance/ta764/chapter/1-Recommendations
SPC: https://www.medicines.org.uk/emc/product/10386/smpc

Galcanezumab (Emgality®)
NICE TA659: https://www.nice.org.uk/guidance/ta659/chapter/1-Recommendations
SPC: https://www.medicines.org.uk/emc/product/10478

Erenumab (Aimovig®)
NICE TA682: https://www.nice.org.uk/guidance/TA682
SPC: https://www.medicines.org.uk/emc/product/9380/smpc

This pathway will be subject to a review in 18 months from the last update or sooner depending on changes in national guidance.

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1. Introduction

1.1 Migraine

Migraine is a primary headache disorder, characterised by episodic headaches accompanied by other symptoms such as photophobia, phonophobia, nausea and vomiting. Migraine can occur with or without aura, which generally features positive or negative visual phenomena, sensory symptoms or speech/language symptoms.

Migraine is relatively common, with a prevalence of around 18% in women and 6% in men. The disease burden is therefore also relatively high, with millions of work days lost to migraine in the UK each year. The impact on quality of life can be substantial, and patients with chronic migraine may also have a high degree of co-morbid disease and high utilisation of emergency healthcare.

Migraine can be described as episodic or chronic:

- Episodic migraine is defined by the presence of headache on fewer than 15 days each month.
- Chronic migraine is defined by the presence of 15 or more headache days each month, of which at least 8 are migraine days.

Around 2.5% to 4% of patients with episodic migraine progress to chronic migraine over the course of a year. Similarly, chronic migraine remits to episodic migraine at a rate of ~26% over the course of two years. The net result is a stable amount of chronic migraine in the general population. Symptoms and clinical imaging are similar in episodic and chronic migraine, so they are thought to share a common pathophysiology.

Treatment of migraine involves pharmacological intervention plus lifestyle advice. Preventative treatment can be considered if the migraines are causing frequent disability, in patients at risk of medication overuse headache, when standard analgesia are not effective or contraindicated, or for uncommon types of migraine. Appropriately taken preventative treatments are likely to be effective in reducing frequency/intensity of migraine, but often do not abort all migraine attacks completely. There are a number of prophylactic agents for migraine available and their use will vary from prescriber to prescriber, reflecting in part the evolving evidence base and their personal experience. Further information on their management in primary care can be found on clinical guideline NICE CG150 and CKS guidance.

Fremanezumab, Galcanezumab and Erenumab belong to a class of monoclonal antibodies specific for calcitonin gene-related peptide (CGRP), a neuropeptide involved in pain signalling, which also promotes vasodilation and inflammation, and have been developed for the prophylaxis of migraine. These drugs compete with CGRP for binding to its receptor, and thereby interrupts the signalling pathway. This class of drug is a positive step forward in providing an alternative treatment option to patients with migraine. The drugs may be more acceptable to patients than Botulinum toxin type A since it can be self-administered as a single injection. By contrast Botulinum toxin A requires attendance at clinic every 3 months, and each treatment consists of multiple injections. Additionally, the anti-CGRP drugs are available via Homecare, allowing for virtual clinics and reduced attendance to the outpatient clinic.

NICE has approved Botulinum toxin type A, Fremanezumab (Ajovy®), Galcanezumab (Emgality®) and Erenumab (Aimovig®) as treatment options for preventing migraine in adults for whom preventative drug treatments have failed. Fremanezumab, Galcanezumab and Erenumab are excluded from the national tariff, but Botulinum toxin type A is no longer a tariff excluded drug.

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2. NICE guidance

2.1 Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (NICE TA260)

Guidance

2.1.1 Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):

- that has not responded to at least three prior pharmacological prophylaxis therapies **and**
- whose condition is appropriately managed for medication overuse.

2.1.2 Treatment with Botulinum toxin type A that is recommended according to 2.1.1 should be stopped in people whose condition:

- is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) **or**
- has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

2.1.3 People currently receiving Botulinum toxin type A that is not recommended according to 2.1.1 and 2.1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

Dose

- The recommended reconstituted dose is 155–195 units, administered intramuscularly as 0.1 ml (5 units) injections to between 31 and 39 sites around the head and back of the neck.
- The recommended re-treatment schedule is every 12 weeks.

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2.2 Fremanezumab for preventing migraine (NICE TA764)

Guidance

2.2.1 Fremanezumab 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 (defined as lack of a clinically meaningful response, intolerance to the treatment or the treatment was contraindicated or unsuitable), and
- the company provides it according to the commercial arrangement

2.2.2 Stop Fremanezumab after 12 weeks of treatment if:

- in episodic migraine (fewer 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%.

NICE committee notes on recommendations:

- Botulinum toxin type A or best supportive care (treatment for the migraine symptoms) is offered to patients whose migraine does not respond to at least 3 preventive drug treatments. Patients who have chronic migraine do not have to have tried Botulinum toxin type A in order to be eligible for Fremanezumab.
- Best supportive care is offered if episodic migraine does not respond to at least 3 preventive drug treatments.
- The clinical trial evidence shows that Fremanezumab works better than best supportive care in both episodic and chronic migraine. However, it is unclear if Fremanezumab works better than Botulinum toxin type A (chronic migraine only).
- For chronic migraine, assuming Fremanezumab works better than Botulinum toxin type A, the most likely cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. Therefore, it is only recommended for chronic migraine.
- For episodic migraine, the estimates of cost effectiveness are even lower, so it is recommended for episodic migraine.

Dose

Fremanezumab is administered as a subcutaneous injection with 2 dosing options:

1. 225 mg once a month, or
2. 675 mg every 3 months (quarterly)

- The treatment benefit should be assessed within 3 months after starting treatment. Any decision to continue treatment should be taken on an individual patient basis.
- Evaluating the need to continue treatment is recommended regularly afterwards.

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2.3 Galcanezumab for preventing migraine (NICE TA659)

Guidance

2.3.1 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 (defined as lack of a clinically meaningful response, intolerance to the treatment or the treatment was contraindicated or unsuitable) and,
- the company provides it according to the commercial arrangement

2.3.2 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%

NICE committee notes on recommendations:

* Treatment options for preventing episodic or chronic migraine include beta-blockers, antidepressants and anticonvulsant drugs. If episodic migraine does not respond to at least 3 oral preventive drug treatments, best supportive care (treatment for the migraine symptoms) is offered. If chronic migraine does not respond to at least 3 oral preventive drug treatments, Botulinum toxin type A or best supportive care is offered.

** For migraine that has not responded to at least 3 preventive treatments, clinical trial evidence shows that Galcanezumab works better than best supportive care in both episodic and chronic migraine. It is plausible that Galcanezumab may work better than Botulinum toxin type A.

*** 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.

Dose

Galcanezumab is administered as a subcutaneous injection with a 240mg loading dose as the initial dose. This is followed by a 120mg Galcanezumab dose injected subcutaneously ONCE a month.

- The treatment benefit should be assessed within 3 months after starting treatment. Any decision to continue treatment should be taken on an individual patient basis.
- Evaluating the need to continue treatment is recommended regularly afterwards.
- Patients should be instructed to inject a missed dose as soon as possible and then resume monthly dosing.

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2.4 Erenumab for preventing migraine (NICE TA682)

Guidance

2.4.1 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 (defined as lack of a clinically meaningful response, intolerance to the treatment or the treatment was contraindicated or unsuitable) and,
- the 140mg dose of Erenumab is used and
- the company provides it according to the commercial arrangement.

2.4.2 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%.

NICE committee notes on recommendations:

* Treatments for preventing chronic or episodic migraine include beta-blockers, antidepressants and antiepileptic drugs. If chronic migraine does not respond to at least 3 preventive drug treatments, Botulinum toxin type A or best supportive care (treatment for the migraine symptoms) is offered. If episodic migraine does not respond to at least 3 preventive drug treatments, best supportive care is offered.

** For people whose migraine has not responded to at least 3 preventive treatments, the clinical trial evidence shows that Erenumab 140 mg works better than best supportive care for preventing chronic or episodic migraine. There is no direct evidence comparing Erenumab with Botulinum toxin type A in chronic migraine, but an indirect comparison suggests that Erenumab has some benefit. It is plausible that Erenumab may work better than Botulinum toxin type A.

*** 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.

Dose

Erenumab is administered as a subcutaneous injection with a 140mg dose injected every FOUR weeks.

- The treatment benefit should be assessed within 3 months after starting treatment. Any decision to continue treatment should be taken on an individual patient basis.
- Evaluation of the need to continue treatment is recommended regularly thereafter.
- The 70 mg dosage is NOT to be used. There is no evidence to support that the 70 mg dosage was clinically effective.

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3. Treatment pathway

3.1 Treatment responses

Aim of treatments is to reduce the frequency, severity or duration of migraine and improve quality of life.

- **Chronic migraine**, a 30% reduction in migraine day (or headache day for Botulinum toxin A) frequency is considered a clinically meaningful response to treatment.
- **Episodic migraine**, a 50% reduction in migraine day frequency is considered a clinically meaningful response.

If clinical response is less than this, or the person is not able to have an adequate dosage for long enough or has adverse events, treatment is stopped and a different preventive treatment option is tried.

As per the NICE TAs for galcanezumab and erenumab, the least expensive drug is to be used unless the alternative is more suitable for the patient. **As of the date of publication of this document, erenumab is the most cost effective anti-CGRP drug.**

3.2 Switching Drug Treatments

3.2.1 Efficacy

There is no clinical evidence to support any difference in efficacy between the different anti-CGRP drugs. The NICE committee concluded that treatment with another anti-CGRP, after failure of a previous anti-CGRP could not be assessed.

Treatment with a second anti-CGRP after failure of a previous anti-CGRP is therefore not recommended.

3.2.2 Intolerance or adverse reaction

The different anti-CGRP drugs have differing mode of action:

- Erenumab – potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor
- Galcanezumab and fremanezumab – bind to the CRGP isoform preventing it from binding to the CGRP receptor

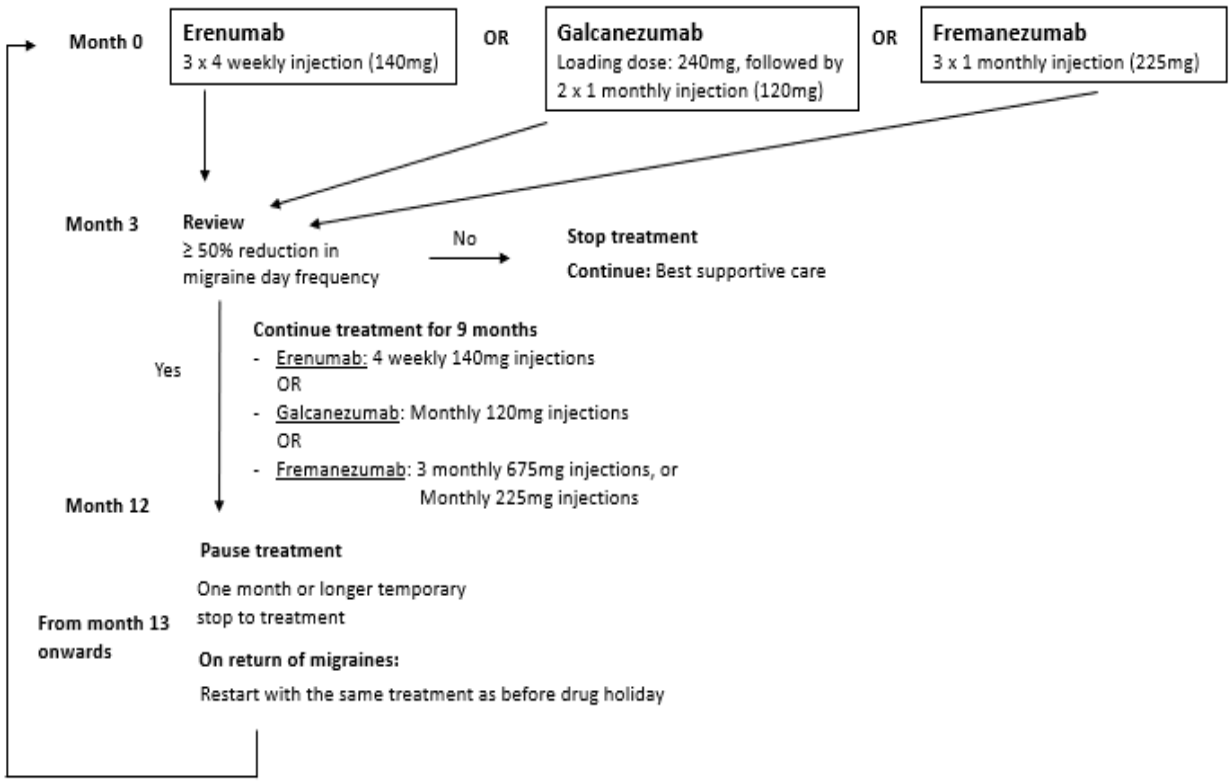
Although switching from one anti-CGRP to another for treatment failure is NOT recommend if a patient develops an intolerance or adverse reaction to the first drug, clinicians may consider using an alternative mode of action drug.

Refractory High Frequency Episodic Migraine:

-4 or more migraine days/month
-at least 3 preventative drug treatments have failed

Erenumab (NICE TA682), Galcanezumab (NICE TA659) OR Fremanezumab (NICE TA764)

The least expensive drug is to be used unless an alternative is more suitable for the patient



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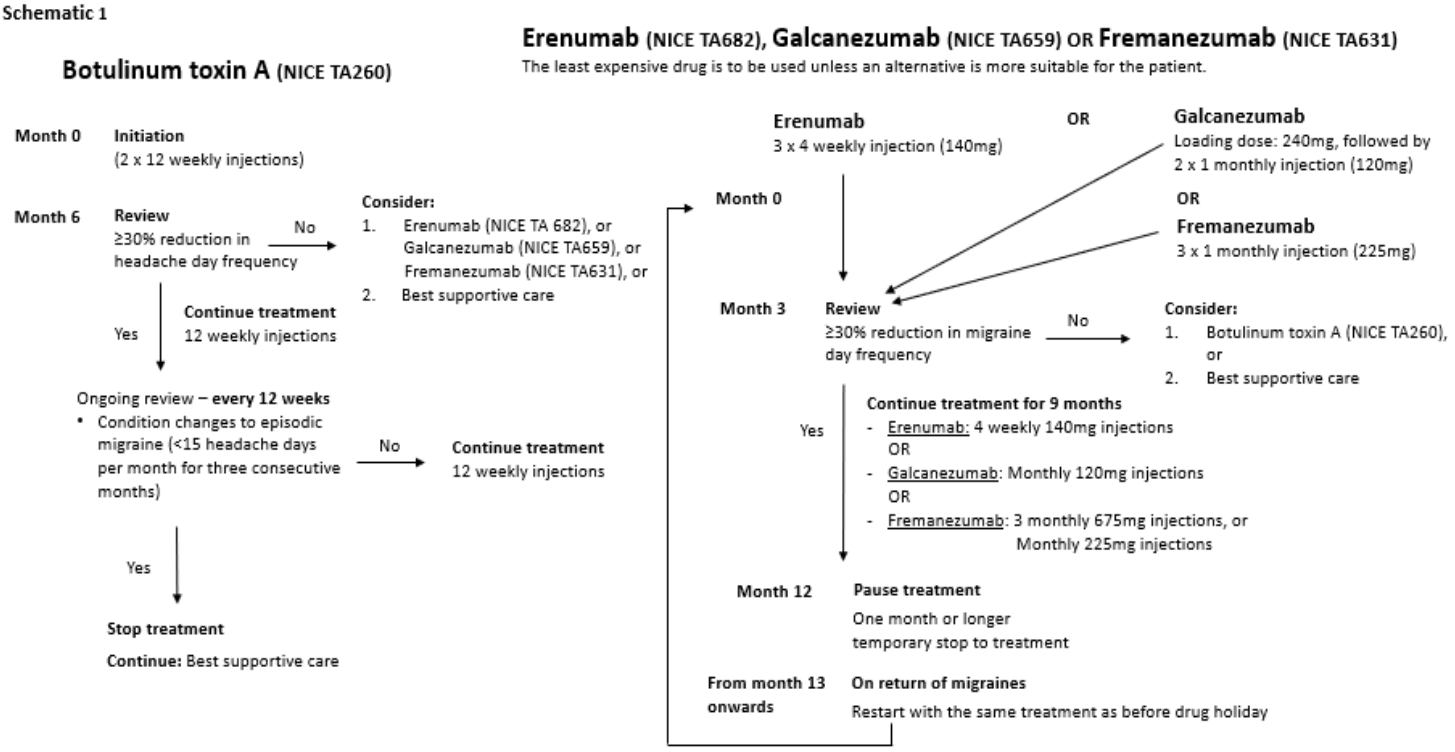
Chronic Migraine

Chronic Migraine: ≥15 headaches days/month with at least 8 of those having features of migraine

New patients To be offered either: Botulinum toxin A, or
antiCGRP: Erenumab, Galcanezumab or Fremanezumab

The choice of agent is guided by:
- Clinical factors (co-morbidites and safety data)
- Patient choice
- Likely adherence

Schematic 1

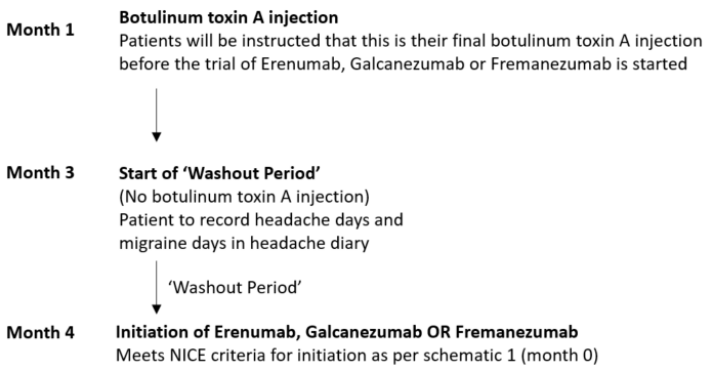


Chronic Migraine: ≥15 headaches days/month with at least 8 of those having features of migraine

For consideration for Current patients on botulinum toxin A for CHRONIC migraine

- Where appropriate, patients who are currently receiving botulinum toxin A therapy can be offered a treatment trial of Erenumab, Galcanezumab or Fremanezumab in line with their respective NICE technology appraisals.
- There will be a washout period of botulinum toxin A before initiating Erenumab, Galcanezumab or Fremanezumab, as per schematic 2 (below)
- Response to Erenumab, Galcanezumab or Fremanezumab - continue as per schematic 1 (above)
- No response to Erenumab, Galcanezumab or Fremanezumab - patient will restart botulinum toxin A as previously prescribed

Schematic 2



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References

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5. Appendices

Appendix 1 - Equality analysis screening tool

Date of assessment	15th March 2021
Assessor name	Geoffrey Howell, Contracts and Commissioning Pharmacist – High Cost Drugs
Name of topic under review	Use of Botulinum toxin type A, and calcitonin gene-related peptide inhibitors for preventing migraine
Purpose of this policy	To inform the prescribing of Botulinum toxin type A, Fremanezumab, Galcanezumab and Erenumab for patients presenting with migraine.

Please outline below any issues that have been identified relating to the topic under policy review that may have an adverse equality impact / health inequality impact on any of the protected groups as defined by the Equality Act 2010.

Protected Group	Issue	Source	Mitigating Actions
Age	Botulinum toxin type A, Fremanezumab, Galcanezumab and Erenumab are licensed for use in adults.		Treatment is restricted for patients 18 years and older.
Disability	None	-	-
Gender	None	-	-
Gender reassignment	None	-	-
Pregnancy / Maternity	The use of Botulinum toxin type A, Fremanezumab, Galcanezumab and Erenumab is not recommended during pregnancy or breastfeeding	SPC	Botulinum toxin type A, Fremanezumab, Galcanezumab and Erenumab will not be used in this cohort of patients.
Race	None	-	-
Marriage/Civil partnership	None	-	-
Religion/Belief	None	-	-
Sexual orientation	None	-	-