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Efgartigimod for treating generalised myasthenia gravis [ID4003]

Technology appraisal committee D – Part 1 slides

4th committee meeting [5th December 2024]

Chair: Raju Reddy

External assessment group: Southampton Health Technologies Assessment Centre

Technical team: George Millington, Alan Moore, Ross Dent

Company: Argenx

History of this topic

There has been 3 previous committee meetings for this topic

ACM1

Key uncertainties:

- Defining the population who would receive efgartigimod in the NHS and the % of IVIg use in this population

ACM2

Key uncertainties:

- Time on treatment for IVIg as the company modelled no discontinuation and maximum dosing

ACM3

Key uncertainties:

- Company did not model a treatment pathway
- Time on treatment for IVIg compared to efgartigimod is uncertain but a key driver of cost-effectiveness

ACM4

Key uncertainties:

- Company did not accept committee preferred assumptions from ACM3, e.g preference to assume equal time on treatment for efgartigimod and IVIg
- Updated PAS and provided alternative analysis, including addition of PLEX

Abbreviations: IVIg, intravenous immunoglobin; PLEX, plasma exchange

Key questions

There are several issues which have a large impact on cost-effectiveness

- Should PLEX treatment be included in the analysis
    - If so, is the company's assumptions around PLEX appropriate?
- What are the most appropriate assumptions around time on treatment for IVIg/PLEX and EFG?
    - In the absence of quality data, should IVIg/PLEX and EFG be assumed have equal time on treatment? If not, what should be considered?
- Is the company's updated treatment pathway appropriate?
- What is the most appropriate modelling inputs:
    - Is a constant 1mg/kg 4 weekly appropriate dosing for IVIg (and PLEX)?
    - What response rate should be assumed for IVIg (and PLEX)?
    - After how many cycles should response be determined?
- Would clinical practice in England follow ADAPT dosing schedule?
- Is there anything else that the committee needs to consider?

Abbreviations: EFG, efgartigimod; IVIg, intravenous immunoglobin; PLEX, plasma exchange

Committee preferences from ACM3

Following ACM3, the committee outlined its preferred assumptions

Committee preferences following ACM3	Included in company ACM4 base case?
IVIg time on treatment should be equal to EFG, in absence of other data	No
IVIg use of 43.8% may be most appropriate estimate but this is uncertain. Dosing of IVIg is also uncertain	Yes
A treatment pathway for MG should be modelled in both model arms	Yes – but company model different pathways for both arms

Abbreviations: ACM, appraisal committee meeting; EFG, efgartigimod; IVIg, intravenous immunoglobin; MG, myasthenia gravis

Background on generalised myasthenia gravis (gMG)

Causes

- Myasthenia Gravis (MG) is an autoimmune disorder caused by Immunoglobulin G autoantibodies targeting acetylcholine receptors (AChRs) and other parts of the neuromuscular junction which impairs neuromuscular transmission → When muscle groups other than the eye muscles are affected, the condition is known as generalised MG (gMG)

Epidemiology

- MG affects about 15 in every 100,000 people in the UK → Around 80% progress to gMG
- About 80% of people with gMG have detectable antibodies against AChRs
- In women incidence peaks between 30 and 50 and in men increases with age

Diagnosis, symptoms and prognosis of gMG

- Diagnosis via physical examination, blood tests and MRI and CT scans
- Symptoms include difficulties with swallowing, vision, speech, breathing, mobility, and fatigue
- Up to 20% of people with gMG experience a myasthenic crisis at least once, where the muscles that control breathing are affected, which requires intensive care support and is the main cause of MG-related deaths

Abbreviations: AChR, Acetylcholine receptor; CT, Computerised tomography; gMG, Generalised Myasthenia Gravis; IgG, Immunoglobulin G; MG, Myasthenia Gravis; MRI, Magnetic resonance imaging; NMJ, neuromuscular junction;

Efgartigimod (Vyvgart, Argenx)

Table: Technology details

Marketing authorisation	• Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are AChR antibody positive • MHRA MA received March 2023
Mechanism of action	• Efgartigimod is a human IgG1 antibody fragment that binds to the neonatal Fc Receptor, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies
Administration	• Efgartigimod is provided as a concentrate for IV infusion and solution for injection • Recommended IV infusion dose is 10 mg/kg as a 1-hour IV infusion administered in cycles of once weekly infusions for 4 weeks • Recommended SC injection dose is 1,000 mg administered in cycles of once weekly injections for 4 weeks • Subsequent treatment cycles are administered according to clinical evaluation → frequency of treatment cycles may vary by patient
Price	• List price: ↳ £6,569.73 per 400 mg vial - treatment cycle: [redacted] – Annual cost [redacted] ↳ £15,307.47 per 1,000mg SC injection – treatment cycle: [redacted] – Annual cost: [redacted] • A simple confidential PAS discount has been agreed for efgartigimod

Abbreviations: AChR, Anti-acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IgG, Immunoglobulin G; IV, Intravenous; MA, Marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, Patient access scheme; SC, Subcutaneous

Company proposed target population

The company outlined the population for which efgartigimod would be used

Company proposed target population

↳ "People with active, refractory disease, with MG-ADL score of 5 or more (over 50% of MG-ADL score from non-ocular symptoms) and who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed.

(Standard treatment includes a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate period of time, at an adequate dose)"

- Company state proposed target population aligns with EAMS population

Abbreviations: EAMS, early access to medicines scheme; MG-ADL, Myasthenia Gravis Activities of Daily Living

Unresolved key issues post ACM3

Table: Unresolved key issues

Issue	Committee's considerations at ACM3	Company post ACM3	EAG comment
PLEX	• Not discussed	• PLEX treatment should be included in both arms – citing expert opinion, established MG pathway and EAMS data	• Unclear methods for implementing PLEX and unclear justification for inputs • Biased in favour of EFG, high PLEX cost for ECM arm
Time on treatment (ToT)	• Did not agree with company that EFG would have much shorter time on treatment • In line with clinical expert input, IVIg ToT should equal EFG, considering lack of data	• Censor people with MG-ADL <5 for IVIg only – time on treatment not equal between EFG and IVIg	• Reasonable people with MG-ADL <5 would not have IVIg • Does not align with committee preference • Very uncertain - further clinical input valuable
IVIg and modelling inputs	• 43.8% appropriate estimate of IVIg use but uncertain • Dosing of IVIg uncertain • Other MG topics ongoing, appropriate consistency important	• 80.5% respond to IVIg • Non-response determined after 3 cycles • IVIg dosing every 4 weeks	• Further clinical input would be valuable

Abbreviations: ACM, appraisal committee meeting; ECM, established clinical management; EFG, efgartigimod; IVIg, intravenous immunoglobin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; PLEX, plasma exchange; ToT, time on treatment

Unresolved key issues post ACM3 (continued)

Table: Unresolved key issues

Issue	Committee's considerations at ACM3	Company post ACM3	EAG comment
Treatment pathway	• Treatment pathway should be modelled	• EFG > IVIg (43.8%) or PLEX (6%) vs • IVIg (43.8%) > PLEX (43.8%)	• PLEX use applied differently in each arm • Should be included as part of ECM basket • Prefer to remove due to how company has included PLEX
Efgartigimod dosing	• Not discussed	• Dosing based on ADAPT trial	• ADAPT dosing schedule not adhered to in EAMS • Clinicians may not base treatment decisions only using MG-ADL score

Abbreviations: ACM, appraisal committee meeting; ECM, established clinical management; EFG, efgartigimod; IVIg, intravenous immunoglobin; MG-ADL, Myasthenia Gravis Activities of Daily Living; PLEX, plasma exchange

Key issue: Inclusion of PLEX treatment

Company include PLEX treatment in new base case, EAG disagree with implementation

Background

- Company originally excluded PLEX from treatment pathway, stating *"a lack of data describing the use of plasma exchange (PLEX) outside the management of acute episodes (exacerbations or myasthenic crisis)"*
- Company now state PLEX treatment should be included in both treatment arms, to reflect the treatment pathway

Company

- Excluding PLEX contradicts established treatment paradigm and clinical opinion
- Other NICE MG appraisals include PLEX as part of ECM and as subsequent treatment

EAG

- Inclusion of PLEX increases costs for comparator arm significantly more than for intervention arm
- All patients who discontinue IVIg in ECM arm receive subsequent treatment with PLEX, only 6% in EFG
- Not enough detail on implementation of PLEX inclusion - such as proportion receiving treatment and for how long, with explanation and justification
- Because of implementation issues, EAG prefer to remove PLEX as subsequent treatment

NICE technical team

- Issues around PLEX are similar to those around IVIg: uncertain uptake, high cost, low QALY gains, uncertain response rate, uncertain time on treatment and dosing; due to limited data

Is the company's inclusion of PLEX appropriate?

Abbreviations: ECM, established clinical management; EFG, efgartigimod; IVIg, intravenous immunoglobin; MG, myasthenia gravis; PLEX, plasma exchange

Key issue: Time on treatment – EFG and IVIg/PLEX

Company include censoring for people with MG-ADL score <5 in new base case

Background

- Company previously included lifetime treatment for IVIg
- At ACM3, clinical experts stated that time on treatment for IVIg compared to EFG was uncertain but did not believe that they would be drastically different – committee preferred to see the same time on treatment assumed for IVIg as EFG as a pragmatic approach

Company

- ToT estimates include censoring people with a MG-ADL score <5 in ADAPT studies – indicates stable disease
- No evidence to support stable disease discontinuation in IVIg arm – plausible explanation for difference in ToT between arms

EAG

- Reasonable that people with MG-ADL <5 would not have IVIg, but note this has a high impact on the ICER
- Unclear on correct time on treatment for IVIg, as evidence is poor - further clinical advice would be helpful

NICE technical team

- Company base case appears to lack face validity – EFG is more effective, licensed and easier to administer but still estimated to have a much-reduced time on treatment vs IVIg/PLEX (~50% less ToT)
- Company base case does not align with current committee preference to equal time on treatment for EFG and IVIg – censoring increases time on treatment for IVIg only (substantially), but not for efgartigimod

NICE

Is the committee preferences still to assume equal time on treatment for EFG and IVIg/PLEX?

Abbreviations: EFG, efgartigimod; IVIg, intravenous immunoglobin; MG-ADL, Myasthenia Gravis Activities of Daily Living; PLEX, plasma exchange; ToT, time on treatment

Key issue: Treatment pathway

Company include differential sequences of treatments across both arms, EAG disagree with implementation

Background

- Company has changed the treatment pathway in the model
- The change assumed differential sequences of treatments across both arms (see diagram on next slide):
  - In efgartigimod arm, only 1 treatment (IVIg or PLEX) assumed after efgartigimod treatment
  - In ECM arm, 43.8% assumed to receive IVIg. After stopping IVIg all are assumed to receive PLEX

EAG

- Disagree with how PLEX was included in the model - applied differently in each arm
- Should have been included in the basket of ECM treatments
- Proportions of people receiving IVIg and PLEX should be the same as for first-line treatment in the ECM arm

NICE technical team

- Unclear why company has changed the treatment pathway assumptions again, beyond addition of PLEX (not in committee preferences after ACM3)
- Company model change means comparison is a sequence of 2 drugs compared to a sequence of 2 drugs – but adding efgartigimod to treatment pathway would lead to a sequence of 3 drugs compared to 2 drugs. Change biases results in favour of efgartigimod and underestimates costs of subsequent treatments in efgartigimod arm

Abbreviations: ECM, established clinical management; EFG, efgartigimod; IVIg, intravenous immunoglobin PLEX, plasma exchange

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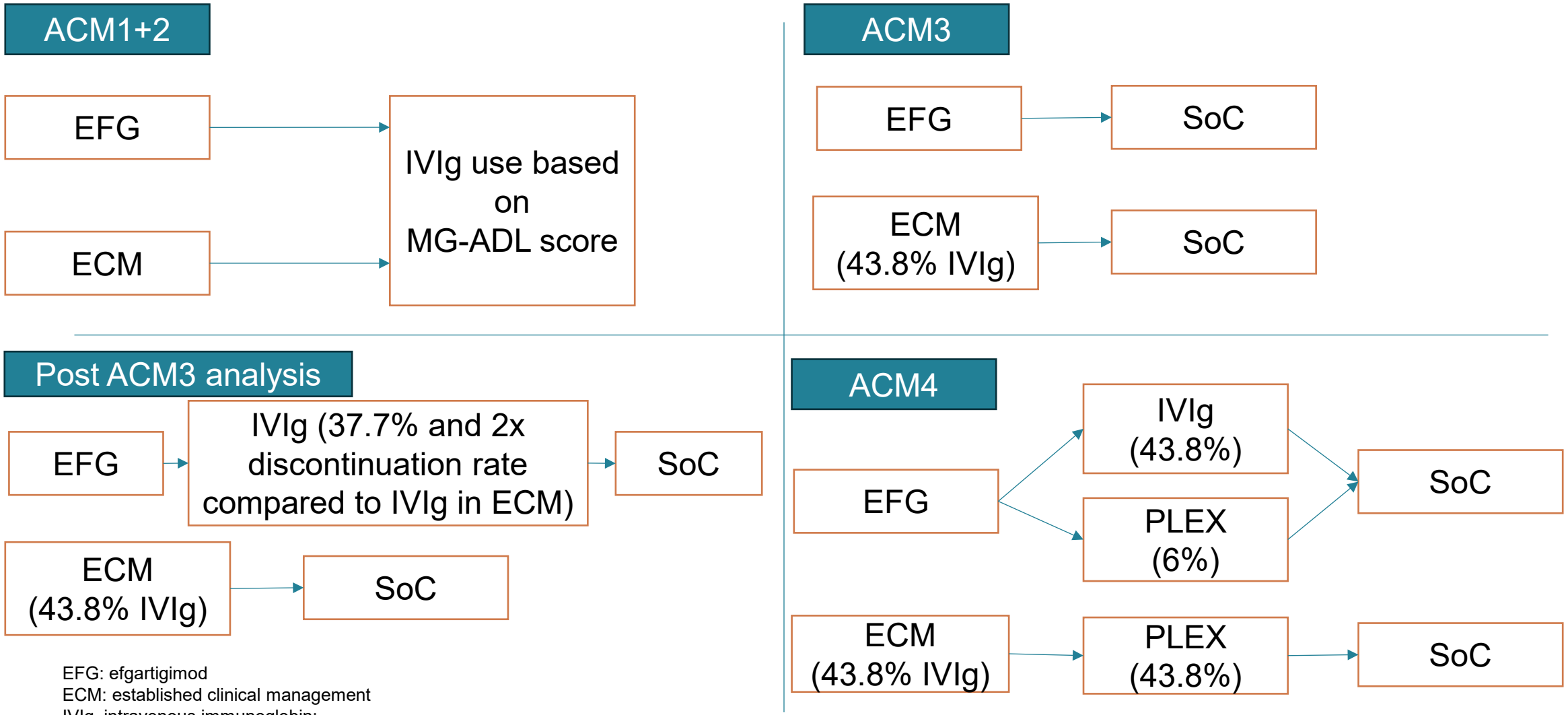
Company treatment pathway history

The company have changed their modelled pathway several times

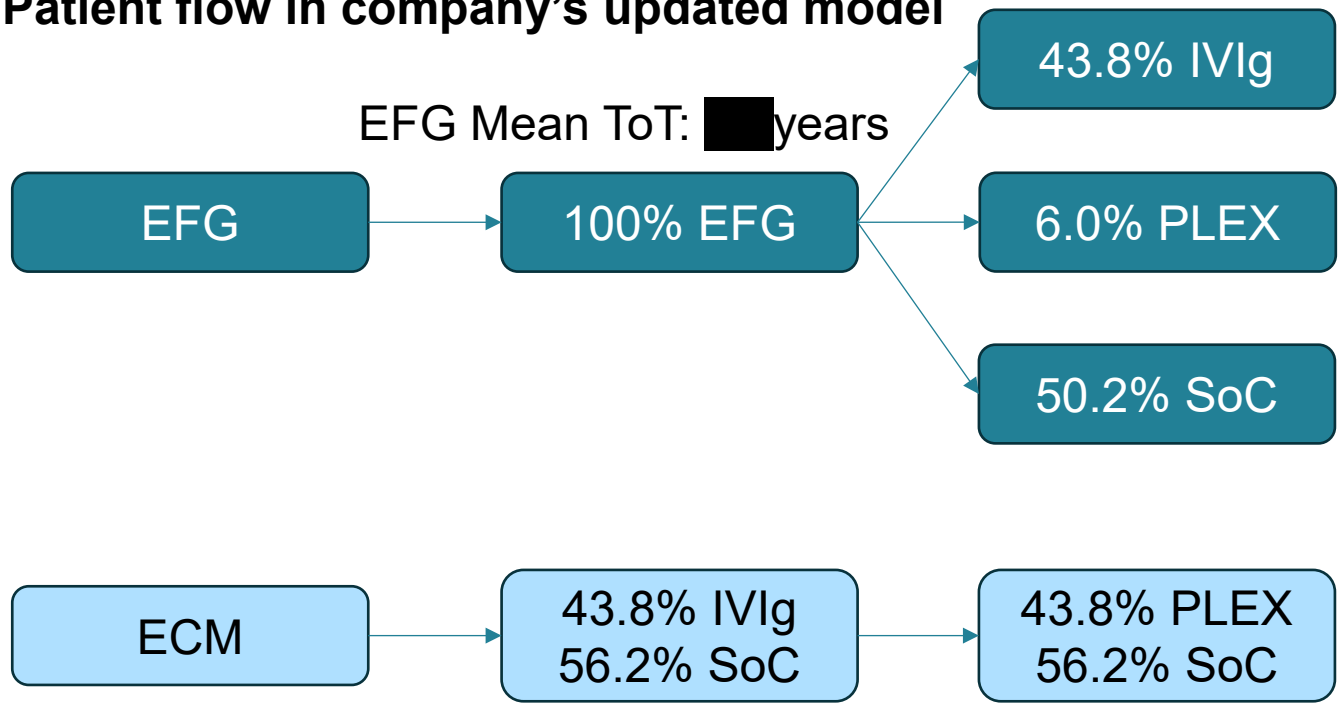


EFG: efgartigimod
ECM: established clinical management
IVIg, intravenous immunoglobin;
PLEX, plasma exchange
SoC: standard of care = includes NSISTS (on-steroidal immunosuppressants) and acetylcholinesterase inhibitors (AChEis)

Key issue: Treatment pathway and time on treatment

Assumptions around treatment pathways and time on treatment for EFG, IVIg and PLEX have a large impact on cost-effectiveness

Patient flow in company's updated model



Model costs when PLEX is included/excluded

	Treatment	Total costs	Drug costs
Company base case **with** PLEX	EFG	[redacted]	[redacted]
	ECM	[redacted]	[redacted]
Company base case **without** PLEX	EFG	[redacted]	[redacted]
	ECM	[redacted]	[redacted]

Company's PLEX inclusion increases drug costs in EFG arm by ~2%, but by ~29% in ECM arm

Mean ToT for IVIg and PLEX:
No censoring = [redacted] years
With censoring = [redacted] years

Is the company's updated treatment pathway for both model arms appropriate?

Abbreviations: ECM, established clinical management; EFG, efgartigimod; IVIg, intravenous immunoglobin PLEX, plasma exchange; SoC, standard of care; ToT, Time on treatment

Model inputs

Several model inputs/assumptions around IVIg/PLEX are made

Background

- There is limited data on IVIg and PLEX use. Several assumptions are required to include these costs in the model; informed by company clinical expert input and selected trial data
- These inputs can impact on cost-effectiveness results

Model parameter (IVIg/PLEX)	Company choice of input	Source
Response rate	80.5%	Hellmann et al. 2014 and Bril et al. 2023
Timing of response	12 weeks (3 cycles)	Company clinical expert input (experts stated between 2-3 cycles)
Dosing	1mg/kg every 4 weeks	Company clinical expert input

Are the company's model inputs appropriate?

Abbreviations: IVIg, intravenous immunoglobin

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Key issue: Efgartigimod dosing

EAMS study suggests ADAPT dosing criteria may not be followed

Background

- In ADAPT, efgartigimod was given once weekly for 4 weeks, followed by 4 weeks off treatment. Subsequent treatment cycles were started once patients lost clinical benefits (MG-ADL score increase to 5 or higher)
- In EAMS (Dionisio et al 2024), efgartigimod was given to people even when MG-ADL score was below 5 – and reported more frequent dosing than ADAPT. Cost-effectiveness results are based on ADAPT dosing

Real world evidence from Dionisio et al 2024 – efgartigimod EAMS dosing

Time period considered	Number of patients[a]	Mean time interval[b]
Time between finishing the 1st cycle and starting the 2nd cycle	32	6.4 weeks (3 - 15.7 weeks, SD 2.4).
Time between finishing the 2nd cycle and starting the 3rd cycle	25	5.5 weeks (3 - 10.9 weeks, SD 1.6)
Time between finishing the 3rd cycle and starting the 4th cycle	14	4.6 weeks (3.0 - 6.7 weeks, SD 0.9).

Decreasing time between dosing cycles

Source: Moniz Dionisio draft paper 2024[1]

SD, standard deviation

[a] Numbers contributing data inferred from the number of patients in Table 2 of the draft paper completing a particular cycle of treatment (i.e.32 patients are listed as completing a 2nd cycle of treatment, so we infer 32 patients started a 2nd cycle of treatment)

[b] Data are believed to be mean, range and SD but the paper does not explicitly state that it is the range that is reported.

Abbreviations: EAMS, early access to medicines scheme; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living

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Key issue: Efgartigimod dosing

EAMS study suggests ADAPT dosing criteria may not be followed

EAG

- Some people in EAMS study appeared to have a treatment cycle after 3 weeks rather than 4
- In practice some patients may receive efgartigimod more frequently than in ADAPT
- Clinicians (and patients) may have a lower MG-ADL score threshold than ADAPT criteria (use in people with MG-ADL scores below 5)
  - Quote from Dionisio paper "*The interval between treatments declined after Cycle 1 – likely because the patient and clinician could predict when the symptoms were likely to deteriorate and adjusted the timing of the next cycle to pre-empt the worsening of symptoms*"

NICE technical team

- Dionisio paper raises generalisability issues for applying ADAPT dosing data to UK population likely to receive efgartigimod. Also ADAPT involved IV administration, whereas subcutaneous administration now available
- Costs for efgartigimod may be underestimated and are subject to high uncertainty
- Costs and outcomes in current analysis are based on efgartigimod only being used if MG-ADL is 5 or above, and would need to be reflected in any potential recommendation
- Company proposed criteria for starting efgartigimod contains an MG-ADL 5 or above criterion, but note that in clinician practice (as in EAMS data) there is potential for subsequent use when MG-ADL is below 5
- EAMS population more representative of the NHS population likely to receive efgartigimod than ADAPT

Is using efgartigimod dosing from ADAPT appropriate in the model?

Abbreviations: EAMS, early access to medicines scheme; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living

Equalities and other considerations

A range of other considerations have been considered by committee

Web comments from ACM3 on equality issues

- Because efgartigimod can be given at a patient's home and is now available as a SC injection it could resolve disparities in access to treatment
- Women develop MG when they are young with increased family and work responsibilities
- Efgartigimod seems to be well tolerated in elderly population who account for the biggest proportion of new gMG diagnoses
  - ↳ Elderly are particularly susceptible to steroid induced side effects and may be more at risk from the thromboembolic complications of IVIg/PLEX

The committee has noted:

- The high unmet need in the company's target population
- MG can impact sustainably on caregivers – and that efgartigimod's impact on this would be considered qualitatively in decision-making

The committee agreed that the maximum acceptable ICER would be at the upper end of the £20,000 to £30,000 per QALY gained range that NICE considers a cost-effective use of NHS resources. But, this would require the areas of outstanding uncertainty to be resolved

Are there any other considerations that committee should take into account?

Abbreviations: MG, myasthenia gravis, SC; Subcutaneous

Unresolved key issues – company and EAG base case

Table: Unresolved key issues - company and EAG base case

Issue		Company	EAG	Scenarios
IVIg	Dosing	1mg/kg every 4 weeks	Same as company – but note ICER increases if clinical expert input is used	• Company clinical expert input • Every 6 weeks
	% non responders	19.5% EFG arm and 19.5% ECM arm	19.5% in both arms	• 30% non-response rate
Time on treatment	Treatment discontinuation (averages)	For EFG = [redacted] years For IVIg/PLEX = [redacted] years (with censoring)	Same as company but note high levels of uncertainty and high impact on ICER – clinical expert input would be valuable	• Equal time on treatment for IVIg and EFG
PLEX	Key assumptions	Include in pathway, with differential use across arms	Remove PLEX from base case	None
Treatment pathway	Treatment sequences	EFG > IVIg or PLEX vs IVIg > PLEX (43.8%)	Same as company but with PLEX removed	None
Other	Efgartigimod dosing	Efgartigimod dosing based on ADAPT trial	Same as company – but note in practice some patients may receive EFG more frequently than in ADAPT	None

Abbreviations: EFG, efgartigimod; IVIg, intravenous immunoglobin; MG, myasthenia gravis; PLEX, plasma exchange

Key questions

There are several issues which have a large impact on cost-effectiveness

- Should PLEX treatment be included in the analysis
    - If so, is the company's assumptions around PLEX appropriate?
- What are the most appropriate assumptions around time on treatment for IVIg/PLEX and EFG?
    - In the absence of quality data, should IVIg/PLEX and EFG be assumed have equal time on treatment? If not, what should be considered?
- Is the company's updated treatment pathway appropriate?
- What is the most appropriate modelling inputs:
    - Is a constant 1mg/kg 4 weekly appropriate dosing for IVIg (and PLEX)?
    - What response rate should be assumed for IVIg (and PLEX)?
    - After how many cycles should response be determined?
- Would clinical practice in England follow ADAPT dosing schedule?
- Is there anything else that the committee needs to consider?

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

- When the company and EAG base case ICERs are calculated using confidential prices both are above what NICE considers an acceptable use of NHS resources

Key model inputs for IVIg/PLEX in MG topics

Summary of current key modelling inputs and comparison with ongoing NICE MG appraisals

	ID4003	ID4008	ID5092
Response rate for IVIg/PLEX	80.5%	Committee asked for more analysis	70% cited by experts – but more analysis needed
Timing of assessment for IVIg/PLEX	12 weeks	3 weeks	3 weeks
Apply costs for IVIg/PLEX	4 weeks	4 weeks	4 weeks (but noted 6 weeks plausible)
Time on treatment & discontinuation	[redacted] years (EFG) [redacted] years (IVIg with new company base case)	Not yet discussed as key issue – time on treatment estimated to be lower for IVIg and PLEX vs ID4003	Not yet discussed as a key issue

ID	
4008	Zilucoplan for treating antibody positive generalised myasthenia gravis
5092	Rozanolixizumab for treating antibody-positive generalised myasthenia gravis

NICE Abbreviations: EFG, efgartigimod; IVIg, intravenous immunoglobin; MG, myasthenia gravis; PLEX, plasma exchange