Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

One Wales Medicines Assessment Group Recommendation
Rituximab for the treatment of myasthenia gravis (OW12)

Date of advice: April 2023
Date of last review: November 2025
AWTTC reference number: OW12

Using the agreed starting and stopping criteria rituximab can be made available within NHS Wales:

- as a first-line add-on treatment for generalised myasthenia gravis in adults;
- as a fourth-line or later treatment option for refractory generalised myasthenia gravis in adults.

The risks and benefits of the off-label use of rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

The choice of rituximab product prescribed should be based on the acquisition cost and in accordance with the One Wales advice on use of biosimilars.

This recommendation has been endorsed by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment decision.

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes

One Wales advice assists consistency of access across NHS Wales.

AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Starting and stopping criteria for rituximab for the treatment of generalised myasthenia gravis

These criteria have been adapted from the NHS England Clinical Commissioning Consultation document (based on refractory use) and with clinical expert advice from Welsh clinicians.

First-line setting

Starting and stopping criteria

Starting criteria:
Rituximab should be made available for the treatment of newly diagnosed **generalised** seropositive MG in combination with corticosteroids. This excludes the treatment of MG confined to the ocular muscles only. Newly diagnosed is defined as generalised symptom onset within the past twelve months. Patients can have ocular symptoms longer than twelve months. Seropositive MG includes both acetylcholine receptor (AChR) positive and muscle specific kinase receptor (MuSK) positive MG. Low titres of AChR antibodies (<20 x 10^{-10} Mol/L) should be interpreted with caution and confirmed by measuring clustered AChR antibody titres.

Screening:
Prior to commencing rituximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Severe heart failure (NYHA class IV)
- Immunoglobulin (Ig) G deficiency (defined as <6 g/L)
- Pregnancy or breast feeding

It is recommended that immunoglobulin levels are determined prior to initiating treatment. The status of varicella zoster immunity should be determined. Caution should be exercised in any patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab[1].

Rituximab should always be initiated by an experienced neurologist, preferably following documented discussion with a clinician experienced in the management of MG and / or a multidisciplinary team discussion.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer considering potential adverse effects,

cautions and contraindications. This consultation should be recorded in the patient's notes.

The recommended rituximab treatment dose regimen for adults with MG in the first line setting is a single dose of 500 mg rituximab administered by intravenous infusion. Repeat single doses of 500mg may be given at six monthly intervals.

Continuing and stopping criteria:
Stopping criteria are based on response to treatment according to predefined efficacy measures. It is important that outcomes are collected for this patient cohort and the outcomes will be reviewed by the One Wales Medicines Assessment Group after 12 months.

Outcome data to determine treatment efficacy:
The following outcome data must be collected to assess a patient's response to treatment:

- MG Composite score and/or the MG Activities of Daily Living (MG-ADL) and/or the MG Quality of Life (MG-QoL) score (at least two of the three outcomes must be recorded at baseline, week 16 and week 24 post treatment)
- steroid requirement at baseline and six months;
- number of admissions to hospital (for MG and other indications)
- need for intravenous immunoglobulin (IVIg) and /or plasma exchange.

Criteria for clinical failure to respond:
If, despite CD19/20 depletion, there is no reduction in clinical improvement (defined as a reduction in MG-ADL / MG composite of at least 2 points), hospital admissions, IVIg courses or plasma exchange requirements or meaningful reduction in steroid dose at 6 months, the patient is a non-responder and rituximab should be discontinued.

Relapse following a period of response to rituximab:
Currently there are no published data on the relapse rate of patients responding to early low dose rituximab treatment. Observational data would predict that the majority of responders to rituximab will lose benefit after a mean of 6-18 months. However, relapse can be delayed for up to 4 years. Patients who are considered responders should be monitored using the criteria detailed above and retreated when symptoms return.

Other considerations:

- Patients should be provided with an alert card stating that they have been treated with rituximab and advised of the symptoms of infection that should prompt urgent medical care
- Immunoglobulin levels should be checked a minimum of 6 monthly
- Treatment with rituximab precludes subsequent treatment with efgartigimod for 6 months

Fourth-line or later setting

Starting and stopping criteria

Starting criteria:
For the purposes of the discussion below, seropositive MG includes both AChR positive and MuSK positive MG. Low titres of AChR antibodies (<20 x 10-10 Mol/L) should be interpreted with caution and confirmed by measuring clustered AChR antibody titres.

Rituximab should be made available for the treatment of generalised MG as a fourth line or later treatment in patients who fulfil the following criteria:

- Seropositive MG patients, who demonstrate active disease despite treatment with maximal immunosuppression:
    - This includes maximal dose of corticosteroids as appropriate, and at least 2 trials of a steroid-sparing immunosuppressant (for example azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus) unless otherwise contraindicated, for an adequate period of time (minimum of 6 months), in an adequate therapeutic dose.

OR

- Seropositive MG patients with crises or frequent relapses:
    - MG patients, with frequent hospital admissions due to MG crisis or significant MG relapses (despite adequate oral immunosuppression as defined above) who require regular treatment with IVIg or plasma exchange, as well as continuing treatment with high doses of corticosteroids as appropriate, and other steroid sparing immunosuppression to achieve stabilisation of symptoms.

OR

- Seropositive MG patients in whom oral immunosuppression is complicated by significant side effects. For MG patients:
    - in whom corticosteroids are relatively contraindicated (for example poorly controlled diabetes, morbid obesity, psychiatric complications).
    - where stabilisation on steroid sparing immunosuppression may be insufficient or delayed.
    - who are intolerant to various steroid-sparing immunosuppressants.
    - who experience multiple and serious infections from oral immunosuppression.

OR

- Seropositive patients whose disease at onset is “explosive”:
    - Patients whose bulbar and respiratory functions are not responding in a timely fashion to high doses of corticosteroids and rescue treatments, including IVIg and/or plasma exchange, and who are unable to wean from ventilatory support in a critical care setting.

OR

- Seropositive patients with significant bulbar weakness who are at risk of aspiration pneumonia:
    - Bulbar weakness may be slower to respond to conventional treatment than other symptoms. Bulbar weakness is a feature of MuSK positive

MG. Where weakness of swallowing muscles persists with an increased risk of chest infection (even if limb weakness has responded to conventional treatment) and IVIg or plasma exchange is required, rituximab can be considered a treatment option.

Screening:
Prior to commencing rituximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Severe heart failure (NYHA class IV)
- Immunoglobulin G deficiency (defined as <6 g/L)
- Pregnancy or breast feeding

It is recommended that immunoglobulin levels are determined prior to initiating treatment. The status of varicella zoster immunity should be determined. Caution should be exercised in any patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab[1].

Rituximab should always be initiated by an experienced neurologist, preferably following a documented discussion with a clinician experienced in the management of MG and / or a discussion by the MG multidisciplinary team discussion.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer considering potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The usual recommended rituximab treatment dose regimen for adults with MG is 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. Repeat courses may be given at six monthly intervals.

Continuing and stopping criteria:
Stopping criteria are based on the literature which suggests that it can take up to 12 months for rituximab to become effective in the management of MG. Having responded, just over half relapse at a mean of 36 months, with efficacy persisting for up to 4 years in more than 40%. The majority of these show an extended response to 2 or 3 cycles of treatment.

Failure to respond to rituximab:
Some patients with a higher clearance of rituximab may not deplete their CD19/20 count and will not respond to a first course of rituximab. Non-responders should have CD19/CD20 counts measured at 4 weeks and where there is no reduction in cell count could be retreated. If a patient has depleted their CD19/20 count but has not

responded to rituximab after 9 months, they should be considered non-responders and no further rituximab treatments given.

Outcome data to determine treatment efficacy:
The following outcome data must be collected to assess a patient's response to treatment:

- MG Composite score and/or the MG Activities of Daily Living (MG-ADL) and/or the MG Quality of Life (MG-QoL) score (at least two of the three outcomes must be recorded at baseline, week 16 and week 24 post treatment)
- steroid requirement at baseline and six months;
- number of admissions to hospital (for MG and other indications)
- need for IVIg and /or plasma exchange

Criteria for clinical failure to respond:
If, despite CD19/20 depletion there is no reduction in hospital admissions, IVIg courses or plasma exchange requirements or meaningful reduction in steroid dose, the patient is a non-responder and rituximab should be discontinued.

Relapse following a period of response to rituximab:
It is expected that the majority of responders to rituximab will lose benefit after a mean of 18 months, but up to 4 years. Patients will be monitored and when symptoms recur, or rising CD19/20 counts are identified, a further course of rituximab could be offered.

Other considerations:

- Patients should be provided with an alert card stating that they have been treated with rituximab and advised of the symptoms of infection that should prompt urgent medical care
- Immunoglobulin levels should be checked a minimum of 6 monthly
- Treatment with rituximab precludes subsequent treatment with efgartigimod for 6 months

References

1. Roche Products Limited. MabThera 100 mg Concentrate for Solution for Infusion. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3801/smpc. Accessed November 2025
2. NHSE Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Available at: https://www.england.nhs.uk/wp-content/uploads/2021/04/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf. Accessed November 2025

AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Review of One Wales Decision – November 2025

Rituximab for the treatment of myasthenia gravis (OW12)

This report was prepared by the All Wales Therapeutics and Toxicology Centre in October 2025. It summarises any new evidence available and patient outcome data collected since the first One Wales review in April 2024.

Background: Rituximab continues to be available in NHS Wales through a One Wales interim decision as an off-label option for the treatment of generalised myasthenia gravis (MG) in adults. It is supported as both a first-line add-on therapy for newly diagnosed seropositive MG and as a fourth-line or later option for refractory disease.

The current One Wales guidance for the treatment of refractory MG recommends a dose of 1,000 mg of rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. Repeat courses may be given at up to six monthly intervals. For first-line use, the One Wales guidance recommends a single 500 mg dose of rituximab by intravenous infusion, repeated 6-monthly, according to response.

Current One Wales Decision: Supported

Licence status: Rituximab is not licensed for treating MG; its use for this indication is off-label.

Guidelines: The 2025 Association of British Neurologists (ABN) guidelines recommends that rituximab as a 500 mg single dose is useful early in the disease course (greater probability of attaining minimal manifestations at week 16 without need for rescue therapies, as per the RINOMAX trial, previously cited in One Wales reports) and can be considered around the time of starting steroids in generalised acetylcholine receptor positive myasthenia gravis (AChR positive MG) with moderate-to-severe disease (Myasthenia Gravis Foundation of America (MGFA) class III or above). The ABN also recommends the use of rituximab for muscle-specific tyrosine kinase receptor positive myasthenia gravis (MuSK positive MG) and early use in those with bulbar symptoms.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines:

TA1069: Efgartigimod for treating antibody-positive generalised myasthenia gravis (not recommended, published June 2025).

ID5092: Rozanolixizumab for treating antibody-positive generalised myasthenia gravis. Draft NICE guidance, published in September 2024, did not recommend the medicine as an add-on to standard treatment, citing uncertainties around long-term outcomes, appropriate comparators, and cost-effectiveness (publication date TBC).

ID4008: Zilucoplan for treating antibody positive generalised myasthenia gravis. Final draft guidance, issued in June 2025, did not recommend the medicine as an add-on to standard treatment, citing uncertainties regarding long-term outcomes, appropriate comparators, and cost-effectiveness. This decision is currently under appeal, with a panel meeting scheduled for November 2025 (publication date TBC).

Effectiveness: A literature search conducted by AWTTC identified one study pertinent to the recommendation, published since the One Wales review in April 2024. A clinical trial with an estimated completion date of 2025 is also reported.

Inan et al. (2024) retrospectively reviewed 16 adults with generalised MuSK positive MG treated with 1000 mg rituximab (2 doses, two weeks apart) after failure or intolerance of prior immunotherapies. Maintenance treatment was administered at intervals of 3—6 months based on clinical evaluation. The mean length of follow-up was 4.8 ± 0.8 years. Rituximab was well tolerated and produced strong outcomes: 81% achieved minimal manifestations or better, 93% discontinued corticosteroids, and 80% of retested patients became antibody negative.

REFINE (NCT05868837) is a phase III, randomised, double-blind, placebo-controlled study evaluating first-line intravenous rituximab (1,000 mg on Days 1 and 15) in adults with generalised AChR positive MG, with a primary endpoint of change in quantitative MG score at 12 weeks, secondary endpoints including corticosteroid tapering and quality of life. The estimated primary completion date was July 2025, but no results have been published at the time of writing this report. This trial is using a higher dosing regimen for first-line treatment with rituximab than recommended in the updated ABN guideline for generalised MG.

Safety: No relevant safety analyses identified in the repeat literature search.

Cost-effectiveness: No relevant cost-effectiveness evidence identified in the repeat literature search.

Budget impact: AWTTC has been provided with data for 18 patients who have received treatment with rituximab since the reassessment in April 2023. In the original evidence summary, clinicians estimated that 40-50 new patients per year across Wales would be eligible for treatment with rituximab for generalised MG. Only two clinicians (covering 3 health board areas) have submitted data and it is expected that additional patients will have been treated with rituximab in the other health board areas. Actual patient numbers are lower than the original budget impact estimates, although outcome data are missing for other health boards it is likely that the overall number of patients treated is less than the original predicted value.

Impact on health and social care services: Minimal.

Patient outcome data:

First-line treatment
AWTTC were provided with outcome data for 16 patients who had received rituximab first-line. Baseline data (before initiation of rituximab) showed that 15 patients had

AChR positive MG [confidential data removed]. Eleven patients were male, and the majority (10/16) were over 60 years old. Thirteen patients were receiving over 10 mg prednisolone daily with eight of these receiving over 20 mg daily. Eleven patients required admission to hospital for their MG in the 12 months leading up to starting rituximab, all but one of whom had received at least one course of intravenous immunoglobulin (IVIg).

Most patients (13/16) received one dose of 500 mg rituximab whilst [confidential data removed]. The number of days between the first rituximab dose and the last clinical review ranged between 35 days to 606 days.

Outcome data for first line use is summarised in Table 1.

Daily steroid dose had decreased at the final follow-up for ten patients after rituximab treatment with follow-up times between 36 and 606 days. Of these ten patients, seven had been admitted to hospital with six requiring IVIg rescue therapy in the 12 months prior to starting treatment with rituximab and none were hospitalised or required rescue IVIg following rituximab treatment up to the last review.

Of the remaining six patients, [confidential data removed].

Quality of life measures generally improved from baseline scores to final follow-up for most patients although reporting was incomplete.

These real world outcome data demonstrate a similar trend in a reduction in both hospitalisations and rescue IVIg treatments in accordance with the results of the RINOMAX study.

Fourth or later line treatment
Confidential data removed.

Evaluation of evidence

The clinical evidence identified since the first One Wales review in April 2024 by an AWTTC literature search supports the continued use of rituximab as a treatment option in line with the current One Wales decision. Limited data on patient numbers makes it difficult to assess budget impact and how it compares to the estimates given in the reassessment in 2023 although it seems likely that patient numbers are significantly lower than originally predicted. Based on available outcome data, first-line rituximab appears to be an effective treatment option for the majority of patients who have received it, allowing a reduction in daily steroid dose, preventing hospitalisations and minimising the need for IVIg rescue treatment. Data on fourth-line use are too limited to analyse response. AWTTC recommends continuing access to rituximab in NHS Wales via the One Wales Medicines process for the treatment of generalised MG as either a first-line option, or a fourth-line or later add-on option.

Next review date: November 2026

References: a full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on the AWTTC website. Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content.

An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified, and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: Evidence Review. Rituximab for the treatment of myasthenia gravis: OW12. 2025.

Table 1: Outcomes for patients receiving first-line rituximab at 500 mg per dose

Confidential data table removed