



AWTTC

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

Rituximab for the treatment of pemphigus and pemphigoid disease in adults and children (OW10)

July 2023

ONE WALES INTERIM DECISION

Rituximab for the treatment of adults and children with pemphigus (excluding pemphigus vulgaris*) after failure of first-line treatments including steroids and steroid-sparing treatments and after failure of third-line treatments for pemphigoid disease including steroids and steroid-sparing treatments

Date of original advice: July 2017

Date of review: July 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government

Rituximab can be made available within NHS Wales for the second-line treatment of pemphigus (excluding pemphigus vulgaris*) and fourth-line treatment of pemphigoid disease in adults and children whose disease has not responded to previous treatments including steroids and steroid-sparing agents.

Rituximab should be prescribed on the basis of lowest acquisition cost.

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.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 3 years or earlier if new evidence becomes available.

*[Rituximab for the treatment of moderate to severe pemphigus vulgaris was recommended for use by AWMSG in October 2022](#) and therefore does not form part of this One Wales interim decision.

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 Group decision.

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

Starting and stopping criteria for rituximab for the treatment of pemphigus (excluding pemphigus vulgaris) and pemphigoid disease in adults and children

These criteria have been adapted from the NHS England Clinical Commissioning Policy document and the British Association of Dermatologists' (BAD) guidelines for the management of pemphigus vulgaris^{1,2}.

Starting criteria (pemphigus variants excluding vulgaris):

Rituximab may be considered after treatment failure with systemic corticosteroids and topical care. Systemic corticosteroid treatment failure is defined as continued disease activity or failure to heal despite three weeks of prednisolone (1.5 mg/kg/day).

Starting criteria (pemphigoid):

Rituximab is a fourth-line option alongside topical care and systemic corticosteroids. Systemic corticosteroids are a well-established and effective treatment for pemphigoid and should be used as first-line therapy, alongside topical care. In the event of corticosteroid treatment failure (defined as above), addition of a steroid-sparing immunosuppressant, either azathioprine or mycophenolate mofetil, may be considered as second line treatment, switching to the alternate as third-line treatment.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This is particularly relevant when considering the use of rituximab in frailer elderly patients and its side effects profile. This consultation should be recorded in the patient's notes.

Rituximab must only be used for treatment in specialised centres, or in collaboration with a specialised centre under the supervision of an expert multidisciplinary team.

The recommended rituximab treatment dose regimen for adults with variants of pemphigus or with pemphigoid 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 up to six monthly intervals.

Continuing and stopping criteria:

Stopping criteria are based on the literature which suggests that it can take up to six months (but more often one to three months) for rituximab to induce complete remission, broadly defined as the absence of new blisters and healing of the majority (> 75%) of lesions (skin and mucosal) for at least two months, with continued remission. If disease control is achieved, further cycles of rituximab should not be given.

Relapse following a period of response to rituximab:

Benefit from a single cycle of rituximab may last 9–18 months or more. A second cycle may be considered in the case of relapse.

Treatment failure:

Treatment failure is defined as continued disease activity or failure to heal, measured up to six months after a cycle of rituximab. Subsequent treatment options may be considered by the team, both in the event of rituximab failing to achieve disease control and also based on assessment of individual patient need.

This is a summary of new evidence available and patient outcome data collected, to inform the review

Background: Pemphigus is a group of rare autoimmune conditions in which painful, fragile blisters occur on the skin and mucous membranes. Types of pemphigus include pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Bullous pemphigoid (BP) is a similar blistering skin disease that tends to affect older people. An [NHS England Clinical Commissioning Policy](#) recommends rituximab for use in adults and children as an option to treat pemphigus or pemphigoid that has not responded to steroids and steroid-sparing agents. Based on unmet need to treat this cohort of patient's rituximab was considered suitable for assessment through the One Wales process.

Current One Wales Decision: [Supported](#)

Licence status: Off-label use for this licensed medicine.

Rituximab is licensed for treatment of pemphigus vulgaris, and is approved in Wales on recommendation of the All Wales Medicines Strategy Group ([AWMSG 1622](#), September 2022). The off-label indication under consideration is for the treatment of all forms of pemphigoid and pemphigus disease, except for the licensed and AWMSG-approved, indication of pemphigus vulgaris.

Guidelines: There have been no relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: No new medicines or HTA advice reported.

Effectiveness: A repeat literature search conducted by AWTTTC identified three papers which analysed the clinical effectiveness of rituximab pertinent to the recommendation (See [Appendix 1](#)). These included two quality of life studies and one retrospective efficacy study.

[Aryanian et al \(2023\)](#) conducted a single centre cross-sectional study including 96 pemphigus patients (12 with pemphigus foliaceus) who received rituximab either 3 months (3M group) prior or within the previous two weeks (R group) of enrolment. The objective of the study was to evaluate the effect of rituximab on health-related quality of life (HRQoL) in pemphigus patients and assess the clinical relevance of the patient-reported outcomes. Generally, the 36-Item Short Form Survey (SF-36) scores were improved with rituximab treatment in all dimensions except for mental health, though these differences were not statistically significant. The mean Dermatology Life Quality Index (DLQI) in the 3M group was significantly lower than the R group (6.96 versus 12.31), ($p = 0.005$) and demonstrated a clinically meaningful improvement in Quality of Life (QoL) for patients in the 3M group. However, this score indicated only a moderate effect on HRQoL which might suggest that the short

duration of treatment in the 3M group was a limitation of this study. The patient general assessment (PGA) scores indicated that patients in the 3M group were significantly more likely to report less severe disease versus the R group ($p = 0.008$). Patients on lower-dose prednisolone had higher QoL measures, suggesting some quality benefit of being able to lower the corticosteroid dose. However, patients were assessed at only one time point, there was no blinding of treatment and the effect of adverse events on QoL was not considered. Results are also not broken down by pemphigus type.

[Rashid et al \(2022\)](#) conducted a single centre observational study which investigated the impact of rituximab on the general and treatment-specific QoL in pemphigus. The study included 47 patients, 18 (38.3%) of which with pemphigus foliaceus, treated with rituximab. Patient reported outcome measurements were collected using DLQI, visual analog scale in pain, Hospital Anxiety and Depression Scale (HADS), and Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL). Rashid et al reported that an improvement in DLQI and TABQOL was observed after 6 and 12 months and suggest that this demonstrates the short-term and long-term effects of the first 2 infusions. They observed a decline in the anxiety scores during treatment stating this may contribute to the positive effect of rituximab treatment. Although no improvement in depression was observed, Rashid et al considers that this may be explained by long-term non-disease-related factors and disease burden. The authors note that a limitation of this study is the absence of the assessment of patient-reported outcome measurements in patients with pemphigus treated with other systemic therapies. Similar to the Aryanian et al study there was no blinding of treatment and results are not broken down by pemphigus type.

The retrospective single centre study by [Bohelay et al \(2022\)](#) assessed efficacy of rituximab treatment in refractory and severe mucous membrane pemphigoid (MMP) in 109 patients with a median follow-up period of 51.4 months. The majority of patients were refractory to immunomodulatory drugs (82.6%) or immunosuppressant agents (66.1%). At baseline 78.0% were receiving an immunomodulator, 4.6% systemic corticosteroids and 15.6% topical corticosteroids. Non-immunosuppressive treatments, such as dapsone and/or salazopyrine (67.9%), had failed in 80.7% of patients, and 66.1% had been administered one or more conventional immunosuppressants, notably cyclophosphamide (50.5%).

Disease control (DC) and clinical response (CR) was achieved in the majority of cases after two cycles of rituximab. These results are similar to efficacy values obtained with rituximab in other autoimmune bullous diseases such as pemphigus. The cumulative proportion of CR (85.3%) was higher than that reported in the systematic review by [Lytvyn et al](#) (70.5%), included in the last evidence review in 2022, whereas the proportion of non-responders was similar (5.4%). Fewer patients had been treated with systemic corticosteroids in this study (11.0%) in comparison with the pooled population from the systematic review (25.1%), however, the proportion of patients receiving immunomodulatory drugs was much higher (78.0% versus 15.1%) so the use of concomitant immunomodulatory drugs might have contributed to the difference in CR between this study and the previous review.

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

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

Budget impact: There were no patients treated in Cardiff and Vale University Health Board in the past 12 months. No information on patient numbers has been provided for the other regions.

Impact on health and social care services: Minimal.

Patient outcome data: No patient outcome data have been received.

Evaluation of evidence

No significant new evidence has been published that challenges the previous evidence presented. AWTTTC recommends to continue access to rituximab in NHS Wales to treat pemphigoid disease and to treat pemphigus (except pemphigus vulgaris).

Next review date: July 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 request by email to AWTTTC@wales.nhs.uk.

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