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)**

**March 2021**

# ONE WALES INTERIM COMMISSIONING 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: March 2021**

**The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.**

Using the agreed starting and stopping criteria, rituximab can continue to 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 is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

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 General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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 Interim Commissioning decision.

**Health board responsibility**
Health boards will take responsibility for implementing One Wales Interim Commissioning decisions and ensuring that a process is in place for monitoring clinical outcomes.

**One Wales advice promotes 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, most commonly inside the mouth, nose, throat and genitals. Pemphigus variants include pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Bullous pemphigoid is a similar blistering skin disease that tends to affect older people. The NHS England Clinical Commissioning Policy recommends rituximab as an option for people with pemphigus or pemphigoid whose disease has not responded to steroids and steroid sparing agents. Based on unmet need to treat this cohort of patients this medicine was considered suitable for assessment via the One Wales process.

**Current One Wales Interim Commissioning Decision**
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. December 2019.

**Licence status**
Rituximab (MabThera®) was granted a licence extension by the European Medicines Agency (EMA) on 11 March 2019 to include the treatment of patients with moderate to severe pemphigus vulgaris[3]. Licence extensions for pemphigus vulgaris have since also been granted to three biosimilars, Rixathon®[4] in August 2019, Ruxience®[5] in April 2020 and Truxima®[6] in June 2019. All of these companies have been contacted to request a submission to AWMSG. In the absence of a submission a statement of advice was issued by AWMSG for MabThera® on June 25th 2019 for this indication[7]. Accordingly the use of rituximab for pemphigus vulgaris is not endorsed by One Wales and this review applies only to other variants of pemphigus and all variants of pemphigoid approved in 2018.

Rituximab for the treatment of adults and children with pemphigus (excluding pemphigus vulgaris) and for pemphigoid disease remains off-label.

**Guidelines**
The International Bullous Diseases Consensus Group published recommendations on the diagnosis and management of pemphigus in March 2020[8]. Rituximab is recommended as a first line treatment option for new onset moderate to severe pemphigus and/or for patients who do not achieve clinical remission with systemic corticosteroids and/or immunosuppressive adjuvants. Responding clinicians in Wales endorse this change in the treatment pathway.

**Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines**
There remain no alternative licensed medicines or health technology appraisal advice for this indication.

**Efficacy/Effectiveness**
The repeat literature search identified six relevant retrospective studies that investigated a variety of indications including pemphigus foliaceus (PF), bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP)[9-14].

Watson et al (2020) analysed clinic data on the efficacy and tolerability of rituximab in patients with both pemphigoid and pemphigus[14]. Patients with MMP (n = 13), BP (n = 4), PF (n = 2), pemphigus vulgaris (PV, n = 13) and epidermolysis bullosa acquisita (n = 1) were treated with 1000 mg rituximab twice, two weeks apart. All patients had taken prednisolone prior to rituximab with the majority having taken at least three different medicines (69.4%). Complete remission (CR) off therapy was reached by 27.3% of all patients (n = 9), while a further 21% had CR on minimal therapy (n = 7). Partial remission (PR) on minimal therapy was achieved by 9.1% (n=3). Median dose of prednisolone was 20 mg (range 10 to 35) prior to rituximab treatment, falling to 4 mg (range

0 to 5) at 12 months and 0 mg (range 0 to 4.35) at 18 months after rituximab treatment. The authors note that the pattern was similar for the three most common diagnoses (MMP, BP and PV)[14].

Dastmalchi et al (2020) investigated the efficacy of rituximab in MMP (n = 24)[10]. Treatment was 500 mg rituximab on day one, then weekly for four weeks. One or more immunosuppressants had been received prior to rituximab treatment with suboptimal effects (n = 20). Disease control was reached by 87.5% (n = 21) after a mean of 4.95 months. Three patients did not reach disease control, with two not reaching disease control despite intravenous immunoglobulin or after rituximab. Relapse was observed in 47.6% (n = 10) after a mean time of 15.2 months. Earlier use of rituximab after diagnosis was associated with quicker disease control[10].

Polansky et al (2019) evaluated clinical outcomes in patients with BP treated with rituximab at a single centre (n = 20)[12]. Treatment was either 1000 mg rituximab twice, two weeks apart, (n = 19) or 375 mg/m2 four times, one week apart (n = 1). All patients were receiving some concurrent therapy at the time of rituximab treatment. Mean follow up after rituximab treatment was 508 days and median time to remission was 196 days, while median time to relapse was 508 days. Durable remission was reached by 75% (n = 15) at mean 169 days. Seven reached CR and eight reached PR with or without adjuvant treatment. Prednisone was no longer taken by 60% of the durable remission group (n = 9)[12].

Kianfar et al (2020) evaluated safety and efficacy of rituximab in paediatric patients (mean age 15, range 10-17 years) with different pemphigus diseases (PV, n = 10; PF, n = 2; BP, n = 1)[11]. Treatment was 375 mg/m2 rituximab one week apart for four doses. Seven patients had received some form of treatment prior to rituximab. Six patients (PV, n = 4; PF, n = 2) received rituximab first line alongside prednisolone. CR on minimal therapy was reached by seven patients, PR on minimal therapy was reached by three patients and CR without adjuvant medication was reached by one patient. Mean time to remission was 3 months (range 2 to 6). Mean duration of remission was 21 months (range 3 to 56). Relapse occurred in nine patients (PV, n = 7; PF, n = 2) after a mean of 23 months (range 7 to 35) and responded to rescue treatment with steroids +/- methotrexate or rituximab[11].

De et al (2020) evaluated the effectiveness of biosimilar rituximab in patients with PV (n = 130) or PF (n = 16)[9]. Treatment was 1000 mg rituximab twice, two weeks apart. CR off therapy was reached by 73.3% of patients (n = 107) at mean 6.6 months after first rituximab treatment. Relapse was experienced by 76.5% of patients after CR off therapy for a mean of 9.1 months. Time taken to reach remission after rituximab use was significantly longer for PF than PV and required higher steroid doses for longer. PF lesions were found to take significantly more time to relapse[9].

Shimanovich et al (2020) evaluated the long term efficacy of rituximab in pemphigus disease (PV, n = 45; PF, n = 14)[13]. Treatment was either 1000 mg rituximab twice, two weeks apart, (n = 46 [PF, n = 10]) or 375 mg/m2 four times, one week apart (n = 13 [PF, n = 4]). Median follow up was 104 months. CR was reached by 73% of patients (n = 43), 39% reaching CR without adjuvant medication (n = 23) and 34% reaching CR with minimal medication (n = 20). Relapse was experienced by 63% of patients who had reached CR (n = 27) at a median of 25 months with 24 of these patients receiving a second cycle of rituximab. PR was reached by 17% of patients (n = 10) and 10% showed no improvement (n = 6). Three patients with PF never reached CR. Long term CR without adjuvant medication was reached by 27% of patients (PV, n = 13; PF, n = 3) with duration median 65 months. Overall rituximab therapy led to a clinical improvement in 58 out of 59 patients in the study[13].

**Safety**

Overall no new safety signals were identified for rituximab in the treatment of pemphigus and pemphigoid disease. In the paediatric study, cerebrovascular thrombosis occurred in one patient after the second infusion in the first treatment cycle, which may have been related to rituximab or the prednisolone the patient was receiving, the patient did not receive the third and fourth rituximab infusion. The same patient experienced septicaemia after a second rituximab infusion in the second treatment cycle[11].

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

**Budget impact**
Clinicians from one health board provided information on patient numbers. Two clinicians have not used rituximab in the last year while a third clinician has used rituximab [Confidential data removed]. The original evidence status report, which included PV, estimated that between six and nine patients would be eligible for rituximab treatment annually (the majority of these patients having PV).

**Impact on health and social care services**
The impact on the service remains minimal.

**Patient outcome data**
Clinicians from one health board provided information on patient numbers. Two clinicians have not used rituximab in the last year while a third clinician has used rituximab for [Confidential data removed]. Clinicians have raised concerns about the absence of PV in the current recommendation as this is one of the main groups of patients that they are likely to present for this treatment. In line with current processes, manufacturers have been requested to submit evidence for appraisal by the All Wales Medicines Strategy Group.

**References**

1. NHS England. Clinical Commissioning Policy: Rituximab for immunobullous disease. Jul 2016. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/04/16035_FINAL.pdf. Accessed Feb 2021.
2. Harman KE, Brown D, Exton LS et al. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017*. *British Journal of Dermatology.* 2017;177:1170-1201. Available at: https://doi.org/10.1111/bjd.15930. Accessed Feb 2021.
3. European Medicines Agency. MabThera®. Procedural steps taken and scientific information after the authorisation. Jul 2019. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/mabthera-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed Dec 2020.
4. Sandoz Limited. Rixathon®. Summary of Product Characteristics. Sep 2020. Available at: https://www.medicines.org.uk/emc/product/2714/smpc. Accessed Nov 2020.
5. Pfizer Limited. Ruxience®. Summary of Product Characteristics. Sep 2020. Available at: https://www.medicines.org.uk/emc/product/11792/smpc. Accessed Nov 2020.
6. Napp Pharmaceuticals Limited. Truxima®. Summary of Product Characteristics. Oct 2020. Available at: https://www.medicines.org.uk/emc/product/8878/smpc. Accessed Nov 2020.
7. All Wales Medicines Strategy Group. Rituximab (MabThera®) 100 mg and 500 mg concentrate for solution for infusion. Reference number: 3192. Appraisal information. Jun 2019. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/rituximab-mabthera2/. Accessed Dec 2020.
8. Murrell DF, Pena S, Joly P et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. *Journal of the American Academy of Dermatology.* 2020;82(3):575-585. Available at: https://doi.org/10.1016/j.jaad.2018.02.021. Accessed Nov 2020.
9. De D, Bishnoi A, Handa S et al. Effectiveness and safety analysis of rituximab in 146 Indian pemphigus patients: A retrospective single-center review of up to 68 months follow-up. *Indian Journal of Dermatology, Venereology & Leprology.* 2020;86(1):39-44. Available at: https://www.ijdvl.com/article.asp?issn=0378-6323;year=2020;volume=86;issue=1;spage=39;epage=44;aulast=De. Accessed Nov 2020.
10. Dastmalchi DA, Moslemkhani S, Bayat M et al. The efficacy of rituximab in patients with mucous membrane pemphigoid. *Journal of Dermatological Treatment.* 2020:1-7. Available at: https://doi.org/10.1080/09546634.2020.1801974. Accessed Nov 2020.
11. Kianfar N, Dasdar S, Mahmoudi H et al. Rituximab in childhood and juvenile autoimmune bullous diseases as first-line and second-line treatment: a case series of 13 patients.

*Journal of Dermatological Treatment.* 2020:1-6. Available at: https://doi.org/10.1080/09546634.2020.1788702. Accessed Nov 2020.
12. Polansky M, Eisenstadt R, DeGrazia T et al. Rituximab therapy in patients with bullous pemphigoid: A retrospective study of 20 patients. *Journal of the American Academy of Dermatology.* 2019;81(1):179-186. Available at: https://doi.org/10.1016/j.jaad.2019.03.049. Accessed Nov 2020.
13. Shimanovich I, Baumann T, Schmidt E et al. Long-term outcomes of rituximab therapy in pemphigus. *Journal of the European Academy of Dermatology & Venereology.* 2020;4:1-6. Available at: https://doi.org/10.1111/jdv.16561. Accessed Nov 2020.
14. Watson N, Carrozzo M, and Hampton P. A retrospective cohort study reporting rituximab treatment for 33 patients with immunobullous disease. *Journal of Oral Pathology & Medicine.* 2020;13(13). Available at: https://doi.org/10.1111/jop.13123. Accessed Nov 2020.