



# 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**

**October 2018 (partial update August 2019)**

### **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: September 2018**

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

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 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.**

## **Background**

Pemphigus vulgaris is a rare autoimmune condition in which painful, fragile blisters occur on the skin and mucous membranes, most commonly inside the mouth, nose, throat and genitals. 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 third-line treatment of pemphigus 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. July 2017.

## **Licence status**

At the time of the original review (October 2018), rituximab for the third-line treatment of pemphigus 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 was off-label. A submission for marketing authorisation for rituximab (MabThera®) to treat pemphigus vulgaris was filed with the European Medicines Agency in February 2018<sup>1</sup>. Marketing authorisation was subsequently granted in March 2019<sup>2</sup>.

## **Guidelines**

The British Association of Dermatologists' (BAD) guidelines for the management of pemphigus vulgaris was updated in November 2017<sup>3</sup>. In summary, the guidelines report that rituximab is effective in newly diagnosed and treatment-resistant pemphigus disease. Rituximab is effective for all forms of pemphigus. The rheumatoid arthritis dosing protocol (1,000 mg dose given twice, two weeks apart) is preferred due to cost considerations, with similar efficacy to the lymphoma protocol (four, weekly infusions of 375 mg/m<sup>2</sup>). The new guidelines place rituximab earlier in the pathway when compared to the current One Wales interim decision. Rituximab is placed as a first line adjuvant immunosuppressant treatment option, as an alternative to azathioprine or mycophenolate mofetil, and combined with corticosteroids, or as a second-line treatment option after failure with first-line corticosteroids and an adjuvant immunosuppressant (which may have included azathioprine or mycophenolate mofetil)<sup>3</sup>. Clinical experts in Wales are supportive of placing rituximab for the treatment of pemphigus as a second-line option based on its greater tolerability and efficacy compared to standard second-line options. NHS England commissioning arrangements, published prior to the updated BAD guidelines in July 2016, place rituximab as a third- and fourth-line treatment option for pemphigus and pemphigoid disease, respectively<sup>4</sup>.

## **Licensed alternative medicines/Health Technology Assessment advice for alternative medicines**

There are no new medicines or health technology assessment advice for this indication since the original One Wales decision.

## **Efficacy/Effectiveness**

A systematic review published in 2018 gives a qualitative review of the sixteen-year history of rituximab therapy for the treatment of pemphigus vulgaris<sup>5</sup>. The review included 1,085 patients. The majority of patients responded well to rituximab therapy and achieved remission within six months. Few patients did not respond well to rituximab and very rarely did patients not show any response or experience disease exacerbation<sup>5</sup>.

The evidence status report had scant clinical effectiveness evidence for treatment of pemphigoid patients, particularly those with bullous pemphigoid (16 patients). The repeat literature search identified a retrospective study which assessed the effectiveness and safety of rituximab in patients (n = 28) with pemphigoid disease who had previously received one or more immunosuppressants with suboptimal effect or with unacceptable side effects<sup>6</sup>. Patients with bullous pemphigoid (n = 8), mucous membrane pemphigoid (n = 14), epidermolysis bullosa acquisita (n = 5) and linear IgA disease (n = 1) were included. Treatment with 500 mg of rituximab (n = 6) or 1,000 mg of rituximab (n = 22) was administered on days 1 and 15. Rituximab was added to pre-existing treatment with a local steroid and/or one or two systemic drugs. Mean total follow up time was 30.3 months (range 2–79; standard deviation [SD] 23.0). Partial remission was achieved by 16 patients (57.1%) at a mean

time of 34.2 weeks (range 9–71; SD 18.1). Six patients (21.4%) also achieved complete remission at a mean time of 59.2 weeks (range 24–85; SD 22.1). The high dose regimen was more effective than the low dose. Four of the five IgA-dominant diseases did not respond to rituximab treatment. After a mean time of 72.5 weeks (range 12–238; SD 63.2) 14 patients (66.7%) relapsed. Seven of the 14 relapsed patients were retreated with rituximab which led to remission in six out of seven patients (85.7%)<sup>6</sup>.

### **Safety**

Overall no new safety signals were identified for rituximab in the treatment of pemphigus and pemphigoid diseases. In the retrospective study, 14 adverse events were reported in 11 (39.3%) pemphigoid cases treated with rituximab<sup>6</sup>. The majority of which were infectious (n = 8). There were five cases of severe adverse events (grade 3 or 4) reported, all of which fully recovered. One patient died due to sepsis which was possibly related to rituximab treatment<sup>6</sup>.

### **Cost effectiveness**

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

### **Budget impact**

Based on data provided by three health boards, the number of patients who have received rituximab for the treatment of pemphigus and pemphigoid disease in the last year is currently below the 6–9 patients estimated in the budget impact section of the original evidence summary report. Moving rituximab to second-line in the treatment pathway based on the updated BAD guidelines for pemphigus is likely to have an impact on patient numbers. However, the patient group is likely to remain small as this is an uncommon disease. AWTTTC-sought clinical expert opinion estimates that there would be around 12 patients with pemphigus eligible for rituximab annually in Wales.

### **Impact on health and social care services**

The impact on the service remains minimal.

### **Patient outcome data**

[Confidential data removed]

### **References**

1. Specialist Pharmacy Service. Rituximab. June 2018. Available at: <https://www.sps.nhs.uk/medicines/rituximab/>. Accessed July 2018.
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3. Harman K, Brown D, Exton L et al. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017. *British Journal of Dermatology*. 2017;177:1170-1207.
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5. Tavakolpour S, Mahmoudi H, Balighi K et al. Sixteen-year history of rituximab therapy for 1085 pemphigus vulgaris patients: a systematic review. *International Immunopharmacology*. 2018;54:131-138.
6. Lamberts A, Euverman H, Terra J et al. Effectiveness and safety of rituximab in recalcitrant pemphigoid diseases. *Frontiers in Immunology*. 2018;9(248).