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

Evidence Status Report: Rituximab for the treatment of pemphigus and pemphigoid disease in adults and children where third- or fourth-line treatments, including steroids and steroid-sparing treatments have failed.

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KEY FINDINGS

Report 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. A small number of people have pemphigus or pemphigoid that does not respond to treatment with systemic steroids or immunosuppressants.

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. This use of rituximab is currently off-label, although a submission for marketing authorisation for rituximab (MabThera®) to treat pemphigus vulgaris is expected. A phase III clinical study of rituximab to treat pemphigus vulgaris is scheduled to complete in 2019.

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from rituximab treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness

The evidence of clinical effectiveness of rituximab to treat pemphigus or pemphigoid comes from systematic reviews, retrospective case studies and case reports. Three systematic reviews of different treatment regimens of rituximab to treat pemphigus showed that, despite differences in outcome assessment, generally high (76% to 95%) rates of complete remission were achieved. The relapse rate ranged from 40% to 50%. Two systematic reviews and a case series of rituximab to treat pemphigoid also showed high rates of complete remission with most patients responding to treatment.

Safety

The most common adverse events reported were serious infections, sepsis, septicaemia and neutropenia. No new safety signals were identified for rituximab in treating pemphigus and pemphigoid. The rates of severe adverse events and mortality reported in the case series and case reports were similar for the different rituximab treatment regimens.

Patient factors

Rituximab is administered by intravenous infusion. Different doses and regimens have been used to treat pemphigus and pemphigoid. NHS England's commissioning policy recommends an adult dose of 1,000 mg on days 1 and 15, a second cycle may be considered following relapse.

Cost effectiveness

No cost-effectiveness analyses were identified in the literature and no UK-based studies were identified. A Canadian cost analysis comparing the costs of treating pemphigus and pemphigoid with rituximab and intravenous immunoglobulin indicated that rituximab was cost-saving when compared to treatment with immunoglobulin reducing costs by around one-third.

Budget impact

Based on an estimated 6–9 patients with pemphigus vulgaris or pemphigoid disease eligible for treatment the acquisition cost of rituximab is between £18,858 and £31,433 in year one. Some patients are already receiving this regimen through Individual Patient Funding Requests and local applications, though accurate figures were not available from the health boards. Administration and treatment of adverse reactions may incur additional costs. Some alternative treatments (for example, intravenous immunoglobulin) are more expensive and also have associated administration costs.

Welsh commercial access agreement

This medicine is currently not licensed for the indication under consideration (i.e. is off-label) and therefore the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine. For that reason, a commercial agreement cannot be offered by the company.

Impact on health and social care services
The impact is expected to be minimal considering the small numbers of patients needing treatment.

Innovation and/or advantages
Rituximab is an additional/alternative treatment for these often severe and debilitating skin diseases.

BACKGROUND

Target group

The indication being considered is third-line treatment of pemphigus and fourth-line treatment of pemphigoid in adults and children whose disease has not responded to previous treatments including corticosteroids and steroid-sparing agents.

Technology

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20 on pre-B and mature B lymphocytes[1]. This binding mediates B-cell lysis by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and also induces cell death by apoptosis[1].

Marketing authorisation date

Rituximab is not licensed to treat pemphigus and pemphigoid disease in adults or children, therefore its use in these indications is off-label. An international phase III clinical study is ongoing comparing intravenous rituximab with mycophenolate mofetil to treat moderate-to-severe active pemphigus vulgaris[2]. It is expected to be completed in September 2019[2]. A submission for marketing authorisation for rituximab (MabThera®) to treat pemphigus vulgaris is anticipated.

The European patent for rituximab (MabThera®) expired in 2013 and the US patent in 2016[3]. Biosimilars are now available.

Dosing

There is no agreed optimal dose regimen for rituximab to treat pemphigus or pemphigoid and several different doses have been used in clinical and case studies. There is no agreed dose for use in children; the doses quoted are for adults. The dose used in the ongoing clinical study (in adults) is 1,000 mg rituximab given by intravenous infusion on days 1 and 15, and repeated on days 168 and 182[2].

Clinical background

Pemphigus and pemphigoid are relapsing autoimmune diseases[4]. The most common pemphigus type is pemphigus vulgaris, which causes blisters on the skin and mucous membranes, most often in the mouth, nose, throat and genitals[5]. Extensive blistering can lead to life-threatening fluid loss, infections and disfigurement[4]. The most common type of pemphigoid is bullous pemphigoid, in which blisters form in the deeper levels of the skin, making them less likely to rupture and cause infection and scarring than pemphigus blisters[4].

Pemphigus and pemphigoid are chronic diseases; bullous pemphigoid is usually more common in older people. One UK study showed a median age at presentation of 80 years for pemphigoid and 71 years for pemphigus vulgaris[6]. Disease-specific mortality from all

immunobullous disorders, including pemphigus and pemphigoid, is estimated to be two- to three-fold higher compared with the general population[6].

Incidence/prevalence

Specialist clinicians consulted by AWTTC estimated that 6–9 people in Wales per year would be likely to be eligible to have rituximab as third-line treatment for pemphigus or as fourth-line treatment for pemphigoid.

Pemphigus and pemphigoid are rare diseases[4]. According to Welsh Patient Episode data there were 25–30 cases of pemphigoid treated in hospitals in Wales during 2015-2016[7]. A UK study estimated an incidence of pemphigus vulgaris of 0.7 per 100,000 person years and an incidence of bullous pemphigoid of 4.3 per 100,000 person years[6].

Current treatment options

Treatments for pemphigus and pemphigoid aim to induce clinical remission, control the disease and prevent relapses[8]. Potent topical corticosteroids should be considered for first-line treatment of (bullous) pemphigoid, especially in localised disease[9] and patients tend to be treated in the community. Systemic corticosteroids are the most established treatment for pemphigus and may be used for bullous pemphigoid too, rapidly improving symptom control[9,10]. In addition to systemic corticosteroids patients receive topical treatments: wound care, emollients, topical steroids and steroid/antiseptic/anti-inflammatory mouthwash[8]. Patients with pemphigus receive a steroid-sparing immunosuppressant (most often azathioprine or mycophenolate mofetil) as adjuvant therapy to reduce the side effects associated with systemic corticosteroids[10]. For those with pemphigoid, an anti-inflammatory antibiotic is given alongside the systemic corticosteroid[9].

In the NHS England Commissioning Policy on the use of rituximab for immunobullous disease, the patient treatment pathway for second-line treatments for pemphigus includes switching to alternative steroid-sparing immunosuppressants or to mycophenolic acid if patients develop gastrointestinal symptoms from mycophenolate mofetil[8]. Third-line treatments include intravenous cyclophosphamide, intravenous immunoglobulin, immunoadsorption and rituximab (two infusions of 1,000 mg given two weeks apart)[8].

For treating pemphigoid, the pathway indicates to add steroid-sparing immunosuppressants (azathioprine or mycophenolate mofetil) as second-line treatment and third-line treatment involves switching to alternative steroid-sparing immunosuppressants[8]. Fourth-line treatments are intravenous cyclophosphamide, intravenous immunoglobulin, immunoadsorption and rituximab (dosed as for pemphigus)[8].

Guidance and related advice

- NHS England Clinical Commissioning Policy (2016) Rituximab for immunobullous disease[8]
- British Association of Dermatologists (2012) Guidelines for the management of bullous pemphigoid[9]
- British Association of Dermatologists (2003) Guidelines for the management of pemphigus vulgaris [currently being updated][10]

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by AWTTC identified three systematic reviews, two retrospective reviews and a small prospective study of rituximab to treat pemphigus; and

two systematic reviews and case series and case reports for rituximab to treat mucous membrane pemphigoid and bullous pemphigoid. An open-label, randomised study of first-line treatment of pemphigus with rituximab plus prednisone was also identified. These studies are briefly described below.

Efficacy

Rituximab to treat pemphigus: systematic reviews and a meta-analysis

Wang et al. (2015) conducted a meta-analysis of efficacy of different dosing regimens of rituximab to treat pemphigus that included 578 people from 30 studies identified by a systematic review[11]. The studies included 26 case series, one randomised comparative study and three comparative studies. Subjects under 18 years were excluded. Patients (496 with pemphigus vulgaris and 82 with pemphigus foliaceus) were grouped into high and low dose regimens. High-dose rituximab regimens (n = 453) included: weekly infusions of 375 mg/m^2 for 3, 4 or 5 weeks; two 1,000 mg doses at a two-week interval; and weekly infusions of 500 mg for four weeks. Low-dose rituximab regimens (n = 52) were: two weekly infusions of 375 mg/m^2; and two 500 mg infusions given 15 days apart. Seventy-three patients received a combined regimen with immunoadsorption. Complete remission was defined as "absence of new lesions with complete healing of old lesions with or without concurrent therapy for at least 2 months"[11].

A summary of key endpoint results is shown in Table 1. For the three comparative studies that assessed high versus low dose rituximab therapy, the pooled odds ratio for complete remission was 1.36 (95% confidence intervals [CI] 0.54 to 3.86; p = 0.56) and for relapse it was 0.33 (95% CI 0.02 to 4.79; p = 0.42)[11]. Multivariate logistic regression and linear regression performed for 213 patients from 17 separate studies showed no significant difference between the high-dose and low-dose groups for: complete remission, time to disease control, time to complete remission on therapy and relapse. However, the high-dose group showed significantly longer duration of complete remission compared with the low-dose group (beta-coefficient 2.57; 95% CI 1.19 to 4.95)[11].

Ahmed & Shetty (2015) analysed treatment outcomes of 499 cases of pemphigus vulgaris treated with rituximab[12]. Most patients were treated with either weekly infusions of 375 mg/m^2 rituximab for 4 weeks (n = 224) or with 500 mg or 1,000 mg rituximab given on days 1 and 15 (n = 209). Table 1 shows the key results. A statistically significantly larger number of patients treated with 500 mg or 1,000 mg rituximab on days 1 and 15 did not receive concomitant therapy and a larger number were in clinical remission off therapy than in the group treated with weekly infusions of 375 mg/m^2 rituximab for 4 weeks[12]. Clinical remission was not defined.

Amber & Hertl (2015) retrospectively evaluated published case reports of 155 people with pemphigus (124 with pemphigus vulgaris), with ages ranging from 4 to 86 years, who were treated with a single cycle of rituximab[13]. Complete remission, defined as the absence of new and/or established lesions for at least 2 months[14], was achieved by 80% of patients[13]. No associations were identified between clinical outcome and age, number of previous treatments, and use of adjuvant medicines. No difference in the rate of patients reaching complete remission was seen between those given a high-dose of rituximab (2 doses of 1,000 mg 2 weeks apart) and those given weekly rituximab 375 mg/m^2 for 4 weeks[13].

Table 1. Overall results of three systematic reviews of rituximab to treat pemphigus

	Wang et al.	Ahmed & Shetty	Amber & Hertl
Number of patients (% with pemphigus vulgaris)	578 (86%)	499 (100%)	155 (80%)
Rituximab treatment regimens	High dose (n = 453): • 375 mg/m^2 weekly for 4 weeks, • Two 1,000 mg doses 2 weeks apart; • 375 mg/m^2 - three or five weekly infusions; • four weekly infusions of 500 mg Low dose (n = 52) • 375 mg/m^2 weekly for 2 weeks • 500 mg given 15 days apart	• 375 mg/m^2 weekly for 4 weeks (n=224) • 500 mg or 1,000 mg on days 1 and 15 (n=209)	High dose: • Two 1,000 mg doses given 2 weeks apart Low dose: • 375 mg/m^2 weekly for 4 weeks
Complete remission rate*	76%	90-95%	80%
Time to complete remission	5.8 months	3–4 months	n/r
Duration of complete remission	14.5 months	n/r	n/r
Relapse rate	40%	50%	n/r
* 'Complete remission' outcome is defined slightly differently in each study n/r: Not reported			

Currimbhoy et al. (2015) conducted a retrospective review of 45 patients aged 19–77 years with pemphigus who were treated with rituximab (two intravenous infusions of 1,000 mg given 2 weeks apart, or weekly infusions of 375 mg/m^2 for 4 weeks) at a single centre in the USA[15]. In total, 38 patients fit the inclusion criteria; 79% had pemphigus vulgaris. If complete remission was not achieved, rituximab 500 mg every 6 months was then given until complete remission. The mean follow-up period was 27 months (±16 months). After the first cycle of rituximab 68% of patients achieved remission within 3 months: remission was complete in 16 patients and partial in 10 patients. The 30 patients who were also taking the corticosteroid prednisone reduced their mean dose from 34 mg/day to 5 mg/day within 3 months. A total of 29 patients needed a second cycle of rituximab treatment because of relapse or not achieving complete remission. There was a mean of 12 months to relapse after each infusion, with fewer patients experiencing relapses after additional infusions. Five patients who achieved sustained remission were lost to follow-up[15].

Two additional small studies conducted in India were identified which support these findings[16,17].

Rituximab as first-line treatment for pemphigus – an open-label randomised study

A prospective, open-label study was conducted at centres in France comparing rituximab plus short-term prednisone with prednisone alone as first-line treatment for pemphigus[18]. A total of 90 patients (aged 18 to 80) with moderate to severe pemphigus disease were randomised to receive either oral prednisone (1.0 or 1.5 mg/kg per day tapered over 12 to 18 months) or 1,000 mg intravenous rituximab on days 1 and 14, and 500 mg rituximab at months 12 and 18, combined with prednisone (0.5 or 1.0 mg/kg per day tapered over 3 or 6 months)[18].

The primary endpoint was the proportion of patients who achieved complete remission off therapy at month 24; this was 41 (89%) patients treated with rituximab plus prednisone compared with 15 (34%) treated with prednisone alone[18]. The relative risk of success was 2.61 (95% CI 1.71 to 3.99; $p < 0.0001$). At 24 months, 11 (24%) patients had relapsed in the rituximab plus prednisolone group and 20 (45%) patients in the prednisolone alone group.

Patients were followed up for 36 months. During the third year, for those patients in complete remission at 24 months, one patient (2%) relapsed in the rituximab plus prednisolone group and four (24%) in the prednisolone-alone group[18].

Rituximab to treat mucous membrane pemphigoid:

Taylor et al. (2015) conducted a systematic review of treatments for mucous membrane pemphigoid which identified two case series[19]. In one series, 25 adult patients were treated with 1–2 cycles of rituximab (375 mg/m^2 weekly for 4 weeks) plus adjuvant therapy (including dapsone, sulfasalazine and topical corticosteroids):17 patients achieved complete remission at 12 weeks after one cycle of rituximab. In a second series, four out of 6 adult patients treated with rituximab plus unspecified adjuvant immunosuppressants achieved complete remission on therapy[19].

Shetty et al. (2012) reviewed rituximab to treat mucous membrane pemphigoid and identified two case series and five case reports with a combined total of 28 patients who were treated with infusions of 375 mg/m^2 rituximab at weekly intervals for four weeks[20]. Overall, 20 patients had a complete response and 3 had a partial response. In the largest case series 12 of 20 patients had a complete response after one treatment cycle, of whom 6 (50%) relapsed[20].

Heelan et al. (2013) reported 8 adults with mucous membrane pemphigoid treated with two intravenous infusions of rituximab 1,000 mg on days 1 and 15[21]. After the first cycle, 5 patients had a complete response off therapy, 1 had a complete response on therapy, 1 had a partial response off therapy and 1 had a partial response on therapy. All patients relapsed; the mean time to relapse was 11.4 months[21].

Rituximab to treat bullous pemphigoid:

Shetty & Ahmed's (2013) systematic review of rituximab to treat bullous pemphigoid identified one case series with 5 patients and eight case reports of 11 patients, including 4 children aged 5 months to 14 years[22]. All patients had disease that had not responded to conventional therapy including corticosteroids and immunosuppressant agents. The rituximab treatment regimens used were: 375 mg/m^2 weekly for 4 weeks (10 patients; 4 patients had modified versions of this regimen) and 1,000 mg rituximab given on days 1 and 15 (2 patients). Overall, 11 patients (69%) had a complete response, defined as "absence of new lesions and healing of previous lesions while on or off systemic therapy" and one patient had a partial response, defined as "healing of less than 50% of lesions present before starting rituximab or occurrence of new transient lesions while on systemic therapy". Among the patients who achieved complete response, more than one cycle of rituximab was needed in 44%. The mean follow-up period was 15.6 months[22].

Safety

Adverse events associated with rituximab, reported in ≥ 1 in 10 patients, include upper respiratory tract infections, urinary tract infections, infusion-related reactions, headache and decreased immunoglobulin M levels[1].

Of the 578 patients with pemphigus reviewed by Wang et al., serious adverse events were reported in 18 patients (3%)[11]. The rates of severe adverse events were similar between the groups treated with high-dose or low-dose rituximab regimens[11]. Severe adverse events in 499 cases of pemphigus vulgaris identified by Ahmed & Shetty included: infections, sepsis, septicaemia and neutropenia[12]. In the case series of 372 patients, the rates of severe adverse events were: 4.8% in those given one cycle of four weekly infusions of 375 mg/m^2 rituximab; 2.1% in those given one cycle of 1,000 mg rituximab on days 1 and 15; and none were reported in those given 500 mg rituximab on days 1 and 15. Mortality rates were 1.6%,

1.0% and none, respectively[12]. Overall, both treatment protocols had similar rates of severe adverse events and mortality[12]. Amber & Hertl's review of rituximab to treat pemphigus did not include an analysis of adverse events[13]. Adverse events recorded by Currimbhoy et al. included mild to moderate infusion site reactions that resolved within hours to days; two patients developed herpes zoster after the first and second infusion, respectively, which resolved after antiviral treatment[15].

Among Shetty and colleagues' case series of 20 patients with mucous membrane pemphigoid treated with rituximab, two patients developed serious infections, one of whom died[20]. In the review of 16 cases of bullous pemphigoid, serious infections occurred in 3 patients, two of whom died of bacterial sepsis; one patient died of cardiac complications 10 days after rituximab infusion[22].

In the randomised study of first-line treatment with rituximab plus prednisone in patients with pemphigus, severe adverse events of grade 3 to 4 were more common in patients treated with prednisone alone (53 events) than in those receiving rituximab plus prednisone (27 events; $p = 0.0021$)[18]. The most common events in both groups were diabetes and endocrine disorder (11 in the prednisone alone group and 6 in the rituximab plus prednisone group), followed by myopathy (10 and 3) and bone disorders (5 and 5)[18].

Clinical effectiveness issues

- There are no results available yet from large, prospective studies of rituximab to treat pemphigus or pemphigoid after failure of previous treatments. The evidence reviewed here is from retrospective case series, case reports and a small prospective study. A clinical study of rituximab to treat pemphigus is under way and is expected to complete in 2019.
- A prospective trial in the first-line setting indicates that rituximab plus prednisolone increases the chance of complete remission as compared to prednisolone alone for people with moderate-to-severe pemphigus. Results show that around two patients would need to be treated with rituximab plus prednisolone rather than prednisolone alone for one additional success. Patients in the combination group also reported fewer side effects, though the doses of steroid used and time to taper were significantly different between groups.
- The three reviews of rituximab for treating pemphigus show heterogeneity in study design, methodology and patient cohorts, including different definitions and reporting outcomes. However, all three reviews showed a positive clinical response to rituximab treatment.
- There is currently no recommended dose of rituximab to treat pemphigus or pemphigoid. The evidence from case series and case reports includes different doses of rituximab given in different treatment protocols. NHS England recommends administering rituximab at a dose of 1,000 mg on days 1 and 15 and this tends to have been the favoured dose submitted through Individual Patient Funding Requests.
- Results of comparative studies of different doses of rituximab in treating pemphigus vulgaris showed a significantly longer duration of complete remission in people treated with high-dose compared with those treated with low-dose rituximab regimens[11].
- Evidence for use in children is limited; this is expected because pemphigus and pemphigoid disease are more prevalent in older people. Treatment of paediatric patients with pemphigus vulgaris was only included in one review; no association between age and clinical outcome was reported[20]. One of the reviews of bullous pemphigoid included four children, three of whom had concomitant immunoglobulin therapy[22].
- For the studies and case series reported in pemphigus vulgaris and mucous membrane pemphigoid the previous treatments received by patients are not consistently reported. Some studies included patients receiving rituximab first-line,

although most studies appeared to include patients who had previously received conventional therapy with corticosteroids and immunosuppressive agents.
- There is little information reported on the use of corticosteroids and immunosuppressive agents after rituximab treatment.

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Cost-effectiveness evidence

Context
Literature search by AWTTC identified two references: one abstract (Heelan K et al. 2013[23]) and the related published paper by Heelan K et al. 2015[24,25].

Heelan et al. 2015 was a retrospective observational chart review of patients with either pemphigus or pemphigoid who had been started on rituximab treatment[24]. The 6-month period before starting treatment was compared to the 6-month period after starting treatment. All patients who had received rituximab infusions to treat autoimmune blistering disease in a Canadian hospital between May 2006 and August 2012 were identified. Patients had a confirmed diagnosis of pemphigus vulgaris (84%), pemphigus foliaceus (8%), bullous pemphigoid (2%), or mucosal membrane pemphigoid (6%), and had received rituximab for refractory disease unresponsive to other treatments. All included patients received rituximab using the fixed dose of 2 x 1,000 mg (days 1 and 15). Unit costs were applied to the resources collected in Canadian dollars, 2013[24].

A total of 89 patients met the inclusion criteria: 58% were female and the mean age at starting rituximab was 48 years (standard deviation 13 years; range 17–75 years)[24]. The total rituximab cost for the first treatment course was $855,659. Aggregate costs of intravenous immunoglobulin (IVIg) before and after rituximab treatment were $3.6million and $1.6million, respectively. Overall, pre-rituximab non-medication costs were higher ($46,715) than post-rituximab costs ($22,978). Patients needed fewer visits to a dermatologist (377 vs. 256 visits), with decreases in the cost of specialist consultations needed ($5,807 vs. $3,234) and other treatments used ($64,548 vs. $48,045)[24].

The overall cohort cost in the 6 months before rituximab treatment was $3.8 million and in the 6 months after rituximab it was $2.6 million[24]. The main cost driver was IVIg, representing 96% of the overall cost before rituximab infusion and 63% of the cost afterwards. The cost per patient was $42,231 in the 6 months pre-rituximab and $29,423 in the 6 months post-rituximab[24].

Health economic issues

No cost-utility analyses were identified in the literature and no UK-based studies were identified. The Canadian cost analysis may not be fully generalisable to the UK. The control group was historical and eligibility criteria may have changed. The authors were unable to calculate adverse events secondary to standard treatment versus rituximab (for example, corticosteroid adverse events, such as diabetes). The costs of prophylactic medications in conjunction with corticosteroids (for example proton pump inhibitors) were not included in the analysis. The 6-month timescale may not capture use of additional rituximab infusions.

BUDGET IMPACT

The list price of rituximab and rituximab biosmilar are between £785.84 (Truxima®) and £873.15 (MabThera®) for a 500mg vial[26]. Table 2 shows the predicted budget impact in

Wales. This excludes VAT and any local contracting agreements. It is estimated that between 6 and 9 patients will be eligible for treatment with rituximab annually. The NHS England Clinical Commissioning Policy states relapse rates of 40–50% occurring between 12 and 18 months after initial treatment; a 45% relapse rate was applied in the analysis to estimate the number of patients treated with a second cycle in year 2 (figures rounded).

Table 2. Estimated medicine acquisition costs in Wales

	Year 1	Year 2	Data source
Rituximab (MabThera®) or rituximab biosimilar (Truxima®): two 1,000 mg doses (1 cycle)	£3,143 – 3,493	£3,143 – 3,493	British National Formulary[26]
Number of patients treated	6 – 9	9 – 13	Clinical expert opinion
Gross medicine acquisition costs	**£18,858 – £31,433**	**£28,287 – £45,404**	

Rituximab is administered by intravenous infusion on two days of a cycle, medicine administration costs and the estimated costs associated with adverse events are estimated in Table 3. The adverse event rate was taken from the NHS England Clinical Commissioning Policy for rituximab for immunobullous disease[8]. Serious adverse events were reported as 2.8% in the pemphigus group treated with a high dose of rituximab. The serious adverse events were: sepsis, pulmonary embolism, neutropenia and deep vein thrombosis. The weighted average cost of non-elective treatment episodes of sepsis, pulmonary embolisms and deep vein thrombosis were used to represent the adverse event costs related to treatment with rituximab[8]. These costs will depend on current service capacity.

Table 3. Estimated administration and adverse event costs in Wales

	Year 1	Year 2	Source
Administration costs per patient (1st dose)	£383	£383	National Schedule of Reference Costs (HRG code SB14Z)[27]
Administration per patient (2nd dose)	£328	£328	National Schedule of Reference Costs (HRG code SB15Z)[27]
Adverse event costs applied to 1st dose	£277 – £416	£277 – £416	National Schedule of Reference Costs for sepsis, pulmonary embolus, and deep vein thrombosis[27]
Number of patients treated	6 - 9	9 - 13	Clinical expert opinion NHS England Clinical Commissioning Policy[8]
Net administration and adverse event costs	**£2,575 – £3,863**	**£3,559 - £5,175**	

Budget impact issues

- The budget impact has not considered the discontinuation of therapy, infusion-associated reactions including fever, rigors, flushing and chills which are more common during first infusions. It is assumed that all patients receive one full treatment cycle.
- Only the costs related to serious adverse events have been included, and this is a weighted average of the potential adverse events because no detailed information was available for adverse event rates for the analysis.
- Mortality rates have not been factored in, but the budget impact analysis is for 2 years only so this is unlikely to cause major effects.

- The analysis does not include concomitant treatments or other healthcare used, such as consultant appointments.
- Comparator treatments have not been considered in the budget impact analysis. The cost of using alternative treatments such as IV cyclophosphamide or IV immunoglobulin are likely to be significant.

Welsh commercial access agreement

This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Comparative unit costs

Annual and pack/vial costs for rituximab and comparators are detailed in Table 4.

Table 4. Examples of medicine acquisition costs

Regimens*	Example doses	Approximate annual cost per patient (pack/vial cost)
Rituximab (MabThera®) 1,000 mg x 2 infusions 2 weeks apart	Concentrate for IV infusion, 10 mg/ml 50 ml vial = £873.15	£3,493
Rituximab (MabThera®) 1,000 mg on days 1, 15, 168 and 182	Concentrate for IV infusion, 10 mg/ml 50 ml vial = £873.15	£6,985
Rituximab biosimilar (Truxima®)	Concentrate for iv infusion, 10 mg/ml 50 ml vial = £785.84	£3,143 (2 doses) £6,287 (4 doses)
Cyclophosphamide Oral 50–200 mg per day	Tablets: 50 mg, 100 = £139	£507 to 2,029
Cyclophosphamide IV 500 mg given monthly	Injection: 500 mg vial = £9.20 1 g vial = £10.66	£110.40
IV human normal immunoglobulin 1.2-2 g/kg divided over 3–5 days every 2–4 weeks for 1–34 cycles	Intratect 20 g (200 ml) = £900	£4,500 to £7,200 per cycle (average male - 83.6kg) £27,000 to £43,200 based on an average of 6 cycles per year

IV: intravenous
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[1,28-31].
This table does not imply therapeutic equivalence of drugs or the stated doses.
*Regimens taken from British Association of Dermatologists' guidelines for the management of pemphigus vulgaris[10].

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Rituximab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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