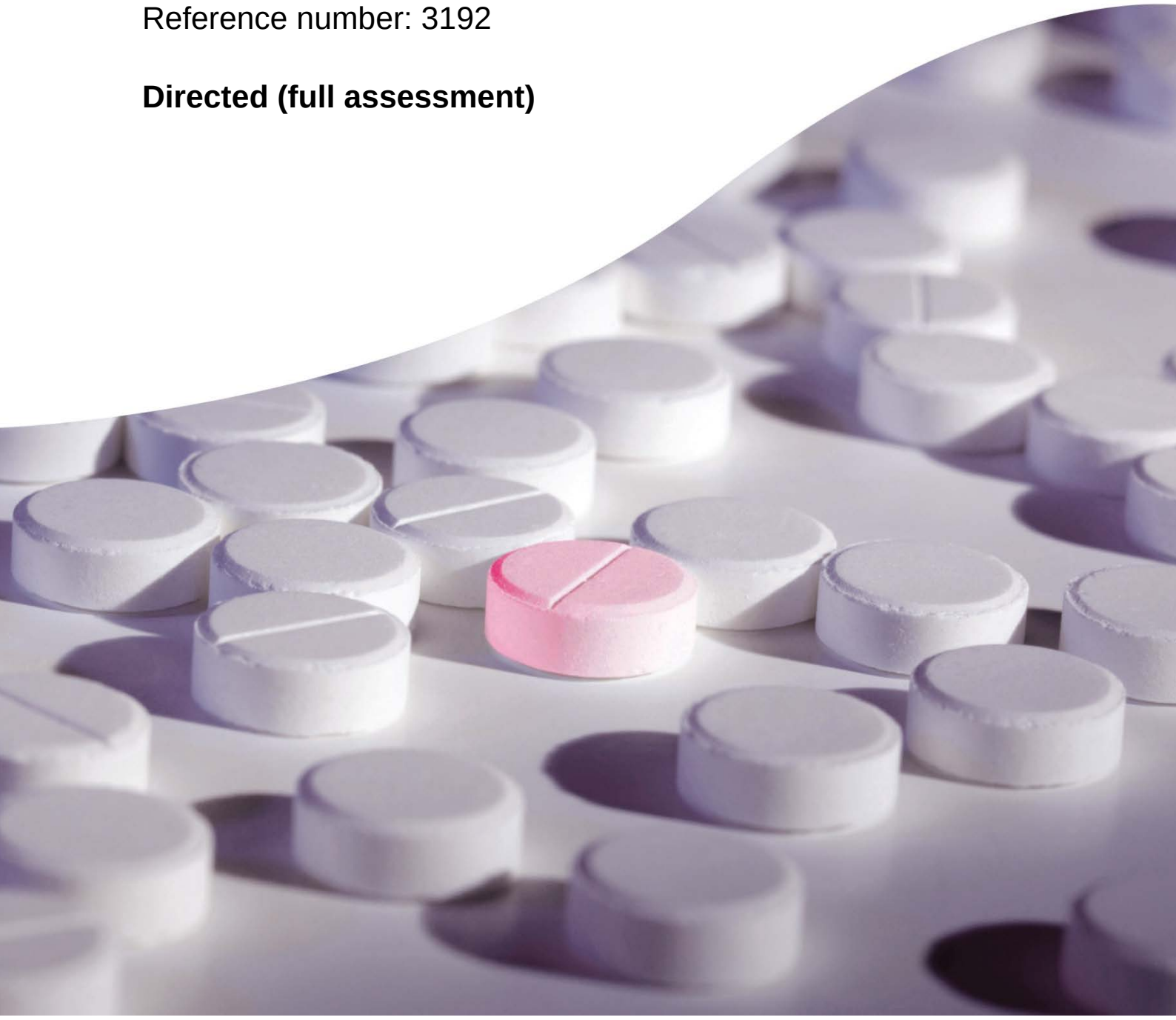
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Rituximab (MabThera®)
100 mg and 500 mg concentrate for solution for infusion

Reference number: 3192

Directed (full assessment)



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
The Routledge Academic Centre
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 218 26900

This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Rituximab (MabThera®) 100 mg and 500 mg concentrate for solution for infusion. Reference number: 3192. September 2022.

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Rituximab (MabThera®) 100 mg and 500 mg concentrate for solution for infusion

1.0 Key facts

Assessment details	Licence extension for rituximab (MabThera®) for the treatment of patients with moderate to severe pemphigus vulgaris.
Current clinical practice	Treatments for pemphigus vulgaris aim to induce clinical remission, control the disease and prevent relapses. Systemic corticosteroids are the most established treatment for pemphigus vulgaris, rapidly improving symptom control. In addition to systemic corticosteroids patients receive topical treatments: wound care, emollients, topical steroids and steroid/antiseptic/anti-inflammatory mouthwash. Patients with pemphigus vulgaris receive a steroid-sparing immunosuppressant (most often off-label azathioprine or mycophenolate mofetil) as adjuvant therapy to reduce the side effects associated with systemic corticosteroids. Welsh clinical experts indicate an unmet need in this population and an absence of any adjunctive treatments for patients with moderate to severe pemphigus vulgaris.
Clinical effectiveness	The main evidence for the efficacy and safety of rituximab in this setting comes principally from two clinical trials; Ritux 3 and PEMPHIX. The Ritux 3 study assessed whether first-line use of rituximab as adjuvant therapy could improve the proportion of patients achieving complete remission off-therapy, compared with corticosteroid treatment alone, while decreasing treatment side-effects of corticosteroids. The findings showed that first-line use of rituximab with short-term prednisone resulted in an almost three times increase in achievement of complete remission off-therapy at month 24 compared with a corticosteroid-alone regimen. Additionally, median cumulative duration of complete remission-off-therapy was more than seven times higher in patients assigned to rituximab plus short-term prednisone. Patients in the rituximab plus short-term prednisone group also took about one-third of the prednisone cumulative dose that the corticosteroid-alone group took, and had about half as many severe adverse events. The PEMPHIX study evaluated the efficacy and safety of rituximab compared to mycophenolate mofetil in adults with moderate to severe pemphigus vulgaris. The study met the primary endpoint at Week 52 and demonstrated

	that rituximab is superior to mycophenolate mofetil, with 40.3% of patients treated with rituximab achieving sustained complete remission without the use of steroids for 16 consecutive weeks or more, compared to 9.5% in the mycophenolate mofetil arm ($p < 0.0001$). All secondary endpoints were statistically significant in favour of rituximab.
Cost-effectiveness	No cost-effectiveness evidence is included in the submission.
Budget impact	It is estimated that 37 patients are eligible to receive treatment with rituximab in Wales in Year 1, decreasing to 27 patients in Year 5. The base case suggests an additional cost of £157,086 in Year 1, decreasing to £51,294 in Year 5. The base case also predicts additional NHS resource use costs valued at £11,520 in Year 1, increasing to £22,473 in Year 5, resulting from the IV administration costs associated with rituximab. The budget impact considerations are based on population estimates provided by clinical experts, which introduces uncertainty. They are also limited to medicine acquisition and administration costs, and outpatient monitoring costs; other resource use, such as those associated with adverse events are not included. The omission of these costs could underestimate or overestimate the resource use associated with the administration of rituximab. The analyses also use the list price for rituximab, which is a standard approach; however, this does not adequately reflect current contract pricing.
Additional factors to consider ***(adapt/add rows if needed)***	Rituximab is the only licensed treatment option for moderate to severe pemphigus vulgaris in the UK. Rituximab is currently approved by NHS England via Clinical Commissioning funding as a third-line treatment for pemphigus. Rituximab (MabThera®) for pemphigus vulgaris was made available for use in NHS Wales by the One Wales process in 2017, but due to licencing of the indication in 2019 it no longer met the criteria and could no longer be endorsed via this route.

This assessment report is based on collaboration with Roche Products Ltd and an evidence search conducted by AWTTC on 22 March 2022.

2.0 Background

2.1 Condition and clinical practice

Pemphigus is a group of rare autoimmune diseases that cause blistering of the mucous membranes and skin. Pemphigus vulgaris (PV) is a rare and potentially life-threatening condition where immunoglobulin G (IgG) antibodies target desmosomal proteins to produce intraepithelial, mucocutaneous blistering[1].

PV is a relapse-remitting condition where there are periods of severe blistering, known as “flare-ups” followed by periods when they heal and begin to fade, when the disease is in remission[2]. The primary lesion of PV is a soft fragile blister filled with clear fluid, in most patients, the blisters start first in the mouth, and appear later on the skin[2]. Other mucous membranes may be affected including the pharyngeal, genital and ocular mucosa[3]. The blisters can erupt easily, leaving areas of raw unhealed skin that are very painful and can increase the risk of infections[4]. Chronic oral lesions can also seriously influence the quality of life, nutritional status, and dental health of patients. Poor dental cleaning due to painful lesions may result in periodontitis[5]. All Wales Therapeutics and Toxicology Centre (AWTTC)-sought patient views reiterated that PV is associated with deterioration of mental health, patients stated they often feel extremely self-conscious, have very low esteem and have sometimes had to leave professional careers due to fatigue, pain and hoarseness/loss of voice. See section 4.2 for more detail on quality of life and productivity studies performed in patients with PV.

Pemphigus can affect people of all ages, but is most common in older people (median age at presentation of 71 years) with a slight female predominance[6]. Pemphigus is estimated to affect anywhere from 0.7-5 people per 1,000,000 per year in the general population[2]. Between 2001 and 2014 there were 29 deaths from PV in England and Wales[7].

There is currently no curative therapy for PV, but treatment can help with symptom control. Remission induction controls the condition in terms of cessation of new lesions formation and the start of healing of established lesions. The 2017 British Association of Dermatologists’ guidelines for the management PV recommends oral prednisolone (pulsed intravenous corticosteroids for severe disease) as a first-line therapy tapered once remission is induced and maintained[1]. This may be combined with an adjuvant immunosuppressant such as azathioprine, mycophenolate mofetil (MMF) or rituximab. A switch to an alternate corticosteroid-sparing agent should be considered as second-line therapy. Adjuvant systemic immunosuppressive drugs can be continued with concomitant use of rituximab, but dose reduction should be considered to decrease the risk of infections and other adverse effects related to immunosuppression. Third-line treatment options include cyclophosphamide, intravenous immunoglobulin (IVIG) and methotrexate, immunoadsorption or plasmapheresis or plasma exchange. When disease control is achieved the consolidation phase begins during which drug doses are continued. At the end of the consolidation phase, when approximately 80% of the lesions (both mucosal and skin) have healed and no new lesion have developed, remission maintenance is initiated by tapering of medicine dose. Treatment is gradually reduced, to the lowest dose required to maintain disease control[1].

Chronic and/or high dose corticosteroid therapy alone results in an estimated remission rate of < 30%[8]. Remission may be short lived. Serious and sometimes fatal

adverse events, resulting from immunosuppression due to long-term use of steroids, may occur [8].

2.2 Medicine

Rituximab is a chimeric, humanised anti-CD20 monoclonal antibody believed to exert its clinical effects in pemphigus through depletion of desmoglein-specific B lymphocytes[8].

Rituximab (MabThera®) was granted marketing authorisation by the European Medicines Agency (EMA) in March 2019 for the treatment of patients with moderate to severe PV[9]. Licence extensions for PV have since also been granted to three biosimilars, Rixathon® in August 2019, Ruxience® in April 2020 and Truxima®[10-12].

The licenced dose in the adult PV population is 1000 mg administered as an IV followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids[9]. A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed. In the event of relapse, patients may receive 1000 mg IV. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion[9].

2.3 Comparators

The comparators identified by AWTTC are:

- azathioprine (Imuran®, Azasan®)
- mycophenolate mofetil (CellCept®, Myfortic®)

2.4 Guidance and related advice

- British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017[1]
- NHS England 2016 Clinical Commissioning Policy: Rituximab for Immunobullous Disease. Ref: 16035/P (Reviewed 2021)[13]

The One Wales Medicines Assessment Group (OWMAG) has previously recommended rituximab can be made available within NHS Wales for the third-line treatment of pemphigus in adults and children whose disease has not responded to previous treatments including steroids and steroid-sparing agents[14]. Rituximab (MabThera®) was granted a licence extension by the EMA in March 2019 to include the treatment of patients with moderate to severe PV. The company did not submit for appraisal by the All Wales Medicines Strategy Group (AWMSG) and therefore a statement of advice was issued by AWMSG for MabThera® for this indication and was removed from the One Wales work programme[15]. One Wales currently recommends the use of off-label rituximab for the treatment of adults and children with pemphigus (excluding PV) 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[14].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, Rituximab (MabThera®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

Evidence for the efficacy and safety of rituximab in this setting comes principally from two clinical trials; Ritux 3 and PEMPHIX[16,17]. Eight relevant publications were also identified during a literature search.

3.1 Ritux 3 study

This is a prospective, multicentre, parallel-group, open-label, randomised trial exploring first-line use of rituximab combined with short-term prednisone versus prednisone alone. It included 90 patients, median age 53 years, randomly assigned to treatment (46 to rituximab plus short-term prednisone and 44 to prednisone alone), 74 (82%) patients in total had newly diagnosed PV[16].

The primary endpoint was the proportion of patients who achieved complete remission off-therapy (CRoff) at month 24, defined as the absence of new or established lesions while the patient had been off corticosteroids for at least two months[16].

Median follow-up for all participants was 729 days (interquartile range [IQR]: 711-744 days) and for patients who did not withdraw from the study was 733 days (IQR 727-749 days)[16].

At 24 months, the proportion of PV patients with CRoff prednisone for two months or more was statistically significantly higher in the rituximab + prednisone arm than in the prednisone arm (34 patients [89.5%] versus 10 patients [27.8%], $p < 0.0001$)[16]. At month 24, no patient in the rituximab plus short-term prednisone group and one patient in the prednisone-alone group were in complete remission and still receiving minimum therapy. Five patients (11%) assigned to rituximab plus short-term prednisone and 28 patients (64%) assigned to prednisone-alone still had active lesions at month 24, or had no lesions but still took a prednisone dose higher than 10 mg/day (relative risks 2.45; 95% confidence interval [CI] 1.64 to 3.67; $p < 0.0001$)[16]. An overview of the secondary endpoints results is detailed in table 1.

The addition of rituximab permitted the rapid tapering of prednisone doses, since about 60% of patients receiving this treatment were able to stop prednisone after six months of treatment, resulting in a seven-fold higher duration of CRoff during the study compared with patients receiving prednisone alone[16].

Table 1. Results in the ITT-PV population from Ritux 3 study[8,16]

	rituximab + prednisone (n = 38)	prednisone (n = 36)
Primary endpoint		
CRoff prednisone ≥ 2 months at 24 months Number of responders (n [%])	34 (89.5)	10 (27.8)
Difference in response rates (p-value)	< 0.0001	
CRoff prednisone ≥ 3 months at 24 months Number of responders (n [%])	34 (89.5)	9 (25.0)
Difference in response rates (p-value)	< 0.0001	
Secondary endpoints		
Number of patients who had at least one severe/moderate relapse a month 24 (n [%])	9 (23.7)	18 (50.0)
CR at month 24 on minimal prednisone treatment (n [%])	34 (89.5)	12 (33.3)
Total cumulative dose of prednisone		
Mean cumulative dose (SD) (mg)	7356.4 (5736.59)	21,845.3 (11,755.81)
Median cumulative dose (min, max) (mg)	5799.5 (2304, 29303)	20520 (2409, 60565)
Duration of CRoff prednisone at 24 months in responders		
Number of responders	34	10
Median duration of CRoff prednisone ≥ 2 months at month 2 (min, max) (days)	496.5 (91, 609)	125.0 (56, 680)
PRO/Quality of Life		
Skindex score at 24 months (mean [SD] change from baseline)	12.3 (-40.5)	21.5 (-37.5)
Mean DLQI score at month 24 (mean [SD] change from baseline)	1.7 (-7.9)	3.6 (-7.4)
CR complete remission; CRoff complete remission off prednisone therapy; DLQI: dermatology quality of life index; ITT intention to treat; PRO: patient reported outcomes; SD: standard deviation		

3.2 PEMPHIX study

This is a phase III, randomised, double-blind, double-dummy, active-comparator, parallel-arm, international, multicentre study designed to evaluate the efficacy and safety of rituximab (MabThera®) compared with MMF in patients with moderate to severe active PV[17]. There were 135 patients aged 23 to 75 years, who were randomly assigned in a 1:1 ratio to receive intravenous rituximab (n = 67) or oral MMF (n = 68) for 52 weeks. Both groups received oral prednisone (or equivalent), which was to be tapered with the aim of discontinuation by week 24. Inclusion criteria included patients receiving standard-of-care corticosteroids, 60 to 120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) and expected to benefit from the addition of immunosuppressive therapy. Patients must not be on current treatments other than glucocorticoids that may be used to treat PV[17].

Patients in the rituximab group received 1000 mg of intravenous rituximab on days 1, 15, 168, and 182 plus twice-daily oral placebo. Patients in the MMF group received

MMF orally twice daily, starting at 1 g per day in divided doses and adjusted to 2 g per day in divided doses by week 2, plus placebo infusions on days 1, 15, 168, and 182 [17].

The primary endpoint at Week 52 was the percentage of participants who achieved sustained complete remission without experiencing treatment failure[17]. Sustained complete remission was defined as achieving healing of lesions with no new active lesions (i.e., Pemphigus Disease Area Index activity (PDAI) score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for at least 16 consecutive weeks, during the 52-week treatment period. [17].

The study met the primary endpoint at Week 52 and demonstrated that rituximab is superior to MMF, with 25 (40.3%) of patients treated with rituximab achieving sustained complete remission, compared to 6 (9.5%) in the MMF arm ($p < 0.001$). All secondary endpoints were statistically significant in favour of rituximab (see table 2). Rituximab had a greater glucocorticoid-sparing effect than MMF, but more patients in this group had serious adverse events[17].

Table 2. Primary and Secondary Efficacy End Points at Week 52 (Modified ITT Population) from PEMPHIX study[17].

	rituximab group (n = 62)	mycophenolate mofetil group (n = 63)
Primary endpoint		
Sustained complete remission (n [%])	25 (40)	6 (10)
Comparison (95% CI) [p value]	31 (15 to 45)* [< 0.001]	
Secondary endpoints		
Cumulative oral glucocorticoid dose (mg)		
Mean	3545	5140
Comparison (95% CI) [p value]	−1595 (−2838 to −353)† [< 0.001]	
Median (range)	2,775 (450 to 22,180)	4,005 (900 to 19,920)
Number of disease flares	6	44
Comparison (95% CI) [p value]	0.12 (0.05 to 0.29)§ [<0.001]	
Time to sustained complete remission — week	NE	NE
Comparison (95% CI) [p value]	4.83 (1.97 to 11.81)¶ [< 0.001]	
Time to disease flare — week	NE	NE
Comparison (95% CI) [p value]	0.15 (0.06 to 0.39)¶ [< 0.001]	
Change from baseline in DLQI score**	−8.87	−6.00
Comparison (95% CI) [p value]	−2.87 (−4.58 to −1.17)†† [< 0.001]	

CI; confidence interval, DLQI; dermatology quality of life index, ITT; intention to treat, NE indicates that the value could not be estimated because the median values were not reached.

*The value is the difference in percentage points.
† The value is the difference in milligrams.
§ The value is the rate ratio adjusted for trial group, region, duration of illness, and baseline PDAI activity score as well as the log of each patient's duration of participation in the trial as an offset.
¶ The value is the hazard ratio.
** Dermatology Life Quality Index (DLQI) scores range from 0 to 30, with higher scores indicating greater impairment.
†† The value is the difference in points.

3.3 Literature overview

A literature search conducted by AWTTC found a network-meta-analysis (included in section 5.3) and ten other relevant publications that had > 20 patients and discussed either safety/efficacy regarding the use of rituximab or quality of life differences among patients with PV. An overview of the ten publications can be found in appendix 1.

Lee et al. conducted a network-meta-analysis (NMA) to determine the best first-line steroid-sparing adjuvants for pemphigus treatment[18]. Ten trials involving 592 patients (548 with PV) were identified through a systematic literature search. Of these identified trials, seven steroid-sparing adjuvants were included in the pairwise meta-analysis of disease remission. Steroid alone was used as a comparator in six of the ten studies, and three studies involved head-to head comparisons of steroid-sparing agents. Among the 7 steroid-sparing adjuvants evaluated, rituximab was the most effective for achieving remission and was more effective than steroid alone (odds ratio, 14.35; 95% confidence interval [CI], 4.71-43.68). Rituximab ranked highest (surface under the cumulative ranking curve (SUCRA), 0.72) with regard to reduction in the probability of disease relapse. Rituximab, azathioprine, and cyclophosphamide pulse therapy enabled the reduction of the cumulative glucocorticoid doses compared to the use of steroid alone: mean differences, -11,830.5 mg (95% CI, -14,089.48 to -9571.52), -3032.48 mg (-4700.74 to -1364.22), and -2469.54 mg (-4128.42 to -810.66), respectively[18].

3.4 Comparative safety

The evaluation of the safety and tolerability of rituximab is based on data from the Ritux 3 and PEMPHIX studies plus supportive data from the full licenced indication[9,16,17]. Data from the Ritux 3 study showed the use of rituximab in combination with low-dose prednisone was well-tolerated and the safety profile in PV patients was consistent with the established safety profile in other approved autoimmune indications[16].

Rituximab is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. Depending on the severity of the IRR and the required interventions, temporary or permanent discontinuation of rituximab is recommended. In most cases, the infusion can be resumed at a 50% reduction in rate when symptoms have resolved[9].

Data from the Ritux 3 study show more severe adverse events of grade 3–4 were reported in the prednisone-alone group (53 events in 29 patients) than in the rituximab plus prednisone group (27 events in 16 patients)[16]. The most common of these events in both groups were diabetes and endocrine disorder (11 [21%] with prednisone alone versus 6 [22%] with rituximab + prednisone), myopathy (10 [19%] versus 3 [11%]) and bone disorders (5 [9%] versus 5 [19%]). Fourteen patients (36.8%) in the rituximab + prednisone arm experienced 43 treatment-related infections and 15 patients (41.7%) in the prednisone arm experienced 28 treatment-related infections[8]. In the rituximab + prednisone arm, 3 patients (7.9%) experienced 5 serious infections. In the prednisone arm, 1 patient (2.8%) experienced 1 serious infection[8]. No patients died during the study[16]. Fourteen patients withdrew from the study: two in the rituximab plus short-term prednisone group (reasons were pregnancy [n = 1] and treatment failure [n = 1]) and 12 in the prednisone-alone group

(reasons were treatment failure [n = 4], treatment adverse events [n = 8] including severe myopathy [n = 2], septic arthritis [n = 1], hip osteonecrosis [n = 1], psychosis [n = 1], chorioretinitis [n = 1], 25 kg weight gain [n = 1], and cardiac failure [n = 1])[16].

Data from the PEMPHIX study reports adverse events occurred in 57 of 67 patients (85%) in the rituximab group and in 60 of 68 (88%) in the MMF group[17]. The most frequent adverse events in the rituximab group were infusion-related reactions (15 patients [22%]), headache (10 patients [15%]), lymphopenia (8 patients [12%]), and upper respiratory tract infection (7 patients [10%]). The most frequent adverse events in the MMF group were diarrhoea (10 patients [15%]) and nasopharyngitis (8 patients [12%]). Serious adverse events occurred in 15 patients (22%) in the rituximab group and in 10 (15%) in the MMF group. Serious infections occurred in six patients (9%) in the rituximab group (pneumonia and upper respiratory tract infection, cellulitis and acute pyelonephritis, pyelonephritis, viral pneumonia, infective bursitis, and skin infection) and in four patients (6%) in the MMF group (pneumonia and influenza, cellulitis and sepsis, herpes zoster, and pyelonephritis). All the patients with serious infections in each group were treated, except in the case of viral pneumonia (which has no specific treatment), and all the cases resolved. In the rituximab group, none of the serious infections resulted in withdrawal from the trial, discontinuation of treatment, or dose modification. In the MMF group, serious infections resulted in discontinuation of treatment in two patients (one of these patients also withdrew from the trial) and in interruption of MMF in two patients. No deaths or cancers occurred in the rituximab group during treatment or up to 18 months after the last dose. One patient in the MMF group who had a history of smoking died on trial day 115 from small-cell lung cancer. In the rituximab group, six patients (9%) discontinued rituximab because of adverse events (infusion related reactions, lumbar vertebral fracture, and pulmonary embolism). A total of six patients (9%) in the MMF group discontinued the trial regimen because of adverse events (cellulitis, pneumonia and influenza together with pulmonary embolism, hyperamylasemia, urinary retention, hepatitis, and the aforementioned small-cell lung cancer). One patient (1%) in the rituximab group and five (7%) in the MMF group had a glucocorticoid related adverse event of grade 3 or higher[17].

3.5 AWTTC critique

- Rituximab meets the criteria for appraisal by AWMSG. OWMAG had to retract endorsement in 2019 due to licencing which restricted a previous access route[14].
- Rituximab is available to patients in England through NHS England Commissioning[13], this means an inequity of access to treatment across the nations.
- Currently in Wales, corticosteroids are the backbone therapy and have central role in the first-line treatment in PV patients. Adjuvant drugs, such as azathioprine and MMF are combined with corticosteroids with the aim of increasing efficacy and reducing maintenance corticosteroid doses and subsequent corticosteroid side-effects. Although mortality and complete remission rates have improved since the introduction of adjuvant drugs, it is acknowledged that there is a lack of prospective randomised clinical trials showing positive efficacy. There remains an unmet clinical need for safer and more effective treatment options for Welsh patients.
- Rituximab is accessible within NHS Wales for the second-line treatment of pemphigus (excluding pemphigus vulgaris) - for patients who do not achieve clinical remission with systemic corticosteroids and/or immunosuppressive

adjuvants[14]. The BAD guidelines advocate the use of azathioprine, MMF, and rituximab as first-line adjuvant therapies. If one of these agents fails to retain remission, switching to alternate first-line adjuvant agent is recommended as a second-line therapy[1] AWTTC-sought expert opinion confirms that rituximab may be used as second line for PV, although some clinicians would reserve this treatment after failure of first-line agents. The pathway in NHS England indicates rituximab as a third line treatment'[13]. Overall, clinicians in Wales indicate that the treatment pathway is changing for PV and more intensive treatments are now preferred earlier in the pathway to induce remission and prevent further relapses.

- Studies have shown that rituximab not only decreased prednisolone intake dramatically but it also provided a shorter time to complete remission when compared to classic immunosuppressive treatments[19]. Rituximab was also found to provide longer disease-free periods compared to classic immunosuppressive therapy[20]. Although these studies have tended to be retrospective in nature.
- The principle side effects of azathioprine include myelosuppression, nausea, hepatotoxicity, hypersensitivity reactions and increased susceptibility to infection. Principle side effects of MMF include gastrointestinal disturbances, lymphopenia, anaemia, neutropenia, thrombocytopenia, increased risk of infections[1]. Generally, studies comparing MMF with azathioprine report there are no significant difference in adverse events, but one did show fewer grade 3 and 4 adverse events with MMF. Infections may also occur with rituximab, including progressive multifocal leukoencephalopathy, reactivation of hepatitis B, and late onset neutropenia [21]. AWTTC-sought clinical opinion states corticosteroid and MMF is likely to remain first-line treatment, rituximab would then be prescribed for refractory or relapsed patients.
- The open-label nature of the Ritux 3 study may have led to bias by overestimation of the beneficial effects of rituximab and/or overestimation of adverse events in the corticosteroid-only treated group. This may also be emphasised further by the primary outcome (clinical remission off corticosteroids for at least two months) relying on physician's clinical judgement regarding the examination of lesions as well as the decisions regarding tapering. This was addressed by adequate training and standardisation of outcome data to try and reduce any bias introduction. The Committee for Medicinal Products for Human Use (CHMP) requested a sensitivity analyses which concluded that it cannot be excluded that bias occurred in favour of rituximab + prednisone. However, the treatment effect was large and the sensitivity analyses show that it is unlikely that the 'real' treatment effect is clinically insignificant. The results of all secondary outcomes were supportive for the results of the primary outcome.
- Limitations of the PEMPHIX study include the small number of enrolled patients with severe or recalcitrant pemphigus and the short duration of follow-up after discontinuation of glucocorticoids. Patients who had a delayed response to either trial drug may have been missed, because the trial design called for glucocorticoid tapering to 0 mg by week 24 and achievement of complete remission that was sustained for at least 16 weeks at the week 52 time point.
- The NMA by Lee et al. is subject to limitations including incomplete data, variable definitions of remission and relapse between trials. Most included trials only compared a single adjuvant with steroid alone or 2 adjuvants

against each other, making comparisons difficult and resulting in wide confidence intervals.

- AWTTC-sought patient submissions highlight the potential for severe side effects and poor response rates with conventional treatments. A few patient submissions stated they were now in remission from receiving a rituximab infusion, with one patient stating they have been in remission for five years which has greatly improved their quality of life. Patients state they were made aware of the safety profile associated with rituximab, but felt all treatments have potential adverse effects and felt their condition was so severe they were willing to accept the potential risks. The benefits of rituximab treatment have been described as 'huge' and 'life changing'.

4.0 COST-EFFECTIVENESS

4.1 Context

A cost-effectiveness analysis has not been submitted.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any cost-effectiveness studies relevant to rituximab versus azathioprine and/or mycophenolate mofetil in the treatment of adult patients with pemphigus vulgaris (PV).

Additionally, no UK-based burden-of-illness studies were identified. However, the review did uncover a retrospective Canadian observational costing study of 89 patients with either pemphigus or pemphigoid (84% of patients had PV)[22]. This before-and-after study concluded that treatment with rituximab is likely to be associated with the lowering of healthcare costs. The costs associated with monitoring, procedures and radiological examinations, access to health care providers and consultations reduced by 39% in the six months after treatment initiation, compared with the six months prior to treatment with rituximab. The average total cost per patient, which additionally included medicine acquisition costs, reduced by approximately 30%. The main cost-driver was a reduction in the use of intravenous immunoglobulins (IVIGs), which accounted for 98% of treatment costs in the 'before' period and 68% in the 'after' period[22]. A French multi-centre study analysed direct healthcare costs associated with first-line rituximab versus corticosteroid treatment in patients with pemphigus[23]. In this study, patients treated with rituximab experienced shorter inpatient stays, and fewer adverse events and relapses. Over the course of three years reductions in costs were also associated with avoidance of IVIGs[23]. A Hungarian study also identified that cost of systemic treatments is the main cost driver from a healthcare provider perspective[24]. In contrast to the aforementioned studies, this was not largely attributed to IVIG usage, as only one patient received IVIG therapy in this study[24].

In terms of the comparative healthcare resource use between rituximab, azathioprine and mycophenolate mofetil in the PV population, no studies were identified with this as a primary focus. A recent retrospective survey, conducted in 235 patients in the United States, focused on rituximab versus other non-biological immunosuppression therapies. The study concluded that there were no differences in medication discontinuation rates secondary to infections or adverse events, or PV-related

hospitalisations[25]. However, this survey had a number of limitations, including the potential for recall bias and a poor response rate.

Although no cost-utility studies were identified, one abstract summarised a Hungarian study designed to elicit health utility values for uncontrolled PV and pemphigus foliaceus and controlled pemphigus from patients using a visual analogue scale (VAS) and time-trade-off (TTO) methods[26]. The authors report the following utilities derived from the VAS and TTO respectively: uncontrolled PV 0.23 (Standard deviation [SD] ±0.24), controlled pemphigus 0.53 (SD ±0.24); uncontrolled PV 0.41 (SD ±0.45), controlled pemphigus 0.66 (SD ±0.36). Whilst there is some variability between the utility scores elicited via VAS and TTO, and the valuation was undertaken by patients as opposed to public, these findings are generally in keeping with the literature, which identifies the notable burden that PV has on patients' health and health-related quality of life (HRQoL)[26]. A pemphigus and pemphigoid US-based registry launched in 2017 identified that 22% of patients reported that their HRQoL was either fair or poor[27]. Patients have reported that they continue to experience poor quality of life despite receiving treatment[25].

A meta-analysis published in 2015 identified 16 papers published between 2000 and 2014, reporting on studies conducted in eight different countries using a variety of tools, including four generic and four disease-specific measures[28]. Notably, the Short Form-36 (SF-36) generic measure was used in eight studies. Although the authors identified lack of any randomised control trials (RCTs) with HRQoL as an endpoint, a lack of prospective cohort studies to inform how HRQoL changes over the course of the disease, and a high variability in reported HRQoL even when the same measurement tool is used (including the SF-36), the analyses reported marked impacts on various aspects of patients HRQoL. On average, patients with PV scored particularly low on the SF-36 questionnaire for the physical, emotional and vitality components of health, with mean scores of 38.1 (95% CI 20.4 to55.9), 47.5 (95% CI 21 to73.2) and 50.7 (95% CI 43.6 to57.7) respectively[28].

In keeping with these findings, a Canadian observational cross-sectional study, also published in 2015, which used the Dermatology Life Quality Index (DLQI) tool to assess the HRQoL of patients with autoimmune bullous dermatoses, identified that the domains most affected by the disease were 'symptoms/feelings' and leisure[29]. The Work Productivity and Activity Impairment Questionnaire- Specific Health problem (WPAIQ-SHP) also identified a significant difference ($p < 0.001$) in activity scores between patients who responded to therapy (11.58, SD ±24.41) and those who did not respond (57.57, SD ±24.41). The level of activity impairment was correlated with a higher percentage of missed work ($r = 0.361$, $p < 0.001$). Despite study limitations, this demonstrates the potential for PV to impact not only on HRQoL but also productivity, thereby highlighting the social impact and burden of the disease[29]. These findings are reflective of a more recent study, which found indirect costs to be higher than the direct costs associated with the disease[24]. A recent Iranian study further identified the negative impacts on carer quality of life, particularly in relation to: emotional distress and depression, physical wellbeing (e.g. amount of rest and sleep), the amount of time spent looking after the patient, time spent enjoying recreation or leisure activities, and the burden of additional household chores[30]. Again, whilst there are limitations to applying these findings to the UK setting, they nonetheless highlight the potential for PV to have a wider impact on family and caregivers.

In terms of comparative HRQoL gains associated with the different treatment options, no studies were found comparing patients with PV when treated with rituximab versus azathioprine. However, the pivotal studies for rituximab did include HRQoL endpoints. The PEMPHIX study, which compared treatment with rituximab versus mycophenolate mofetil in patients with moderate and severe PV, measured HRQoL with the Dermatology Quality of Life Index (DLQI), as a secondary endpoint[17,31], and the 3-level European Quality of Life–5 Dimensions (EQ-5D-3L) as an exploratory outcome[17]. At 52 weeks from baseline there was a statistically significant improvement in DLQI when treated with rituximab compared to mycophenolate mofetil (-8.87 versus -6.00, p = 0.0012). In post-hoc analyses, from which it is not possible to draw firm conclusions, 61.7% of patients treated with rituximab and 25% treated with the comparator achieved a DLQI score of 0, suggesting no effect of disease on HRQoL[31]. Exploratory analyses also identified higher EQ-5D-3L VAS scores at week 52 in patients receiving rituximab (25.93 (SD ±35.65)) versus mycophenolate mofetil (22.93 (SD ±32.34))[32]. There were also differences in the proportion of patients reporting no problems at 52 weeks in the usual activities (83% versus 66.7%), pain/discomfort (76.6% versus 37%) and anxiety/depression (76.6% versus 48.1%) domains of the EQ-5D-3L[32]. Again, no firm conclusions can be drawn from these analyses. However, a single centre observational study published in 2022, supports these findings[33]. It found that rituximab had a marked effect on HQRoL impairments, and levels of pain and anxiety[33]. The Ritux 3 study, which compared treatment with rituximab in combination with prednisolone versus prednisolone alone in patients with pemphigus, also identified greater improvements in DLQI in patients treated with rituximab (p = 0.0411)[16].

5.0 BUDGET IMPACT

5.1 Context and methods

An AWTTC generated budget impact analysis predicts that there will be 37 people with moderate to severe PV in Year 1, increasing to 81 in Year 5. This projection is based on prevalence and incidence estimates provided by Welsh clinical experts. To calculate the number of people who will be prescribed rituximab in Wales it is assumed that all patients with moderate or severe PV are eligible for treatment. Patients receive two 1 g doses of rituximab,14 days apart, followed by two additional 500 mg doses at months 12 and 18. This regimen is in line with the licensed dosing recommendations[9]. Relapse is also factored-in from Year 3 onwards, guided by rates reported in the Ritux 3 pivotal study[16]. Patients who relapse receive an additional 1 g dose of rituximab, in line with the Summary of Product Characteristics (SPC)[9]. An assumed market share for rituximab of 100% is applied from each year, as advised by Welsh clinical experts. The medicines displaced by the introduction of rituximab are azathioprine and mycophenolate mofetil, reflecting current prescribing practices in Wales. It is assumed that patients prescribed these therapies receive ongoing daily treatment. Medicine acquisition costs are taken from British National Formulary (BNF) for rituximab and NHS Tariff for the comparators[34,35]. All patients are modelled to attend four outpatient appointments per year, for monitoring purposes. When initiated on treatment with rituximab, two of these visits are assumed to coincide with initial treatment administration. The same logic is applied for the relapse treatment administration visit. Sensitivity analyses explore the impact of alternative assumptions for rituximab treatment duration, including one additional 500 mg dose at month 24, and an omission of the 500 mg dose at month18.

5.2 Results

The projected budget impact is presented in Table 4. It is estimated that introducing rituximab would lead to an overall cost of £157,086 in Year 1, decreasing to £51,294 in Year 5. This estimate incorporates cost differences resulting from the complete displacement of azathioprine and mycophenolate mofetil.

Sensitivity analysis exploring the impact of assuming a ±500 mg dose for rituximab resulted in lower net medicine acquisition costs in Years 2 to 5, reducing to £41,690 in Year 5 when the month 18 dose was removed; and higher net medicine acquisition costs in Years 2 to 5, increasing to £60,899 in Year 5 when an extra 500 mg is administered at month 24.

Table 4. Costs associated with use of rituximab for the treatment of pemphigus vulgaris

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	37	48	59	70	81
Uptake of new medicine (%)	100%	100%	100%	100%	100%
Number of patients receiving new medicine allowing for remission and relapse	37	48	31	34	27
Medicine acquisition costs in a market without new medicine	£4,446	£5,869	£7,136	£8,559	£9,826
Medicine acquisition costs in a market with new medicine	£161,532	£80,330	£73,344	£62,867	£61,120
Net medicine acquisition costs	£157,086	£74,460	£66,208	£54,307	£51,294

The model estimates that net resource implications arising from the introduction of rituximab will lead to a cost of £11,520 in Year 1, increasing to £22,473 in Year 5. This is a consequence of the intra-venous (IV) administration costs associated with rituximab. These resource-type costs are included for potential planning purposes but may not be realised in practice. Sensitivity analyses exploring the impact of alternative rituximab treatment duration resulted in the lowering of net resource costs in Years 2 to 5, to £21,978 in Year 5 when the 500 mg dose at month 18 is omitted. When an extra 500 mg dose is included at month 24 in the regimen, this results in increased net resource costs in Years 2 to 5, with a cost of £22,968 in Year 5.

5.3 AWTTC critique

- The eligible patient numbers are based on Welsh clinical expert estimates. The literature relating to prevalence and incidence of PV, and the proportion of patients with moderate and severe disease, is sparse and varied. Whilst the modelled estimates are considered plausible by AWTTC, there remains some uncertainty around these figures.

- The budget impact considerations are limited to acquisition, administration and planned outpatient visit costs only. The analysis does not examine how net resource use may be affected by the differences in efficacy and adverse events between the three treatments. The PEMPHIX study suggests that rituximab offers superior efficacy to MMF, has a favourable corticosteroid sparing effect, but is associated with higher frequency of serious adverse events (22% versus 15%)[17]. A Cochrane systematic review, which identified two RCTs comparing mycophenolate mofetil and azathioprine, concluded that azathioprine has a comparatively favourable corticosteroid-sparing effect[21,36,37]. However, mycophenolate mofetil achieved a higher proportion of disease control in one of the studies[21]. This study also found that patients treated with mycophenolate mofetil had a lower rate of grade 3 and 4 adverse events[21]. In contrast, the other study included in the systematic review found no significant differences in adverse events[37]. More recently, a retrospective analysis of medical records in Australia reported the distribution of treatment related adverse events experienced by 21 PV patients receiving prednisolone, rituximab, azathioprine and mycophenolate mofetil[38]. Overall, rituximab was associated with the lowest incidence of adverse events and the most favourable steroid sparing treatment in terms of quality of life[38]. Whilst this observational study offers a potentially useful comparative insight into these treatments, it is subject to notable limitations, including underpowered analysis and dosing of rituximab that is lower than the licenced dose, and anticipated dosing regimen in Wales. A network meta-analysis-based comparison of first-line steroid sparing adjuvants in the treatment of PV and PF, which included rituximab, azathioprine and mycophenolate mofetil, concluded that rituximab is likely to be the best choice in terms of disease remission, steroid-sparing effect, reduction in relapse and adverse-event related treatment withdrawal. However, this analysis was subject to a number of limitations. Most of the trials included compared only one adjuvant to steroid treatment alone. There was also heterogeneity between studies in terms of primary and secondary outcome definitions and disease severity. The resultant estimates and wide credible-intervals demonstrated notable uncertainty[18].
- The analysis uses list price for rituximab. However, All-Wales discounts are available for this medicine. If these are applied in the model, the net medicine acquisition costs are lower than reported in the base case. There are also generic versions of this medicine available.
- The model assumes that all rituximab patients experience remission at 18 months, and only those that relapse in year three receive any further IV treatment. If this assumption underestimates the duration of treatment for rituximab, it has the potential to bias the results of the analyses. Sensitivity analyses explore the impact of an extended treatment duration for patients.
- The model does not capture the costs of adjuvant corticosteroids, which are applicable to all treatment options. This omission compromises the completeness of the budget impact analyses, but is unlikely to introduce decision-making bias. However, the model also does not consider the use of IVIGs. If use of IVIGs is affected differently by the usage of each of the medicines considered in the model, its omission may bias the results of the analysis.
- It is assumed that all patients are monitored four times a year. If treatment with rituximab reduces the required frequency for monitoring, this assumption is likely to bias against rituximab in the analyses.

- Although the regimen used in the model reflects the license for rituximab, Welsh clinical experts suggest that standard practice may involve one fewer 500 mg administration. If this is the case, the analysis may overestimate the costs associated with rituximab. Sensitivity analyses explore the impact of this suggested alternative regimen.

References

1. 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. Accessed April 2022.
2. National Institute for Health Research Innovation Observatory (NIHRIO). Rituximab for Pemphigus vulgaris. 2018. Available at: https://www.io.nihr.ac.uk/report/rituximab-for-pemphigus-vulgaris/. Accessed April 2022.
3. Rashid H, Lamberts A, Diercks GFH et al. Oral Lesions in Autoimmune Bullous Diseases: An Overview of Clinical Characteristics and Diagnostic Algorithm. *American Journal of Clinical Dermatology.* 2019;20(6):847-861.
4. National Health Service. Pemphigus vulgaris. 2018. Available at: https://www.nhs.uk/conditions/pemphigus-vulgaris/. Accessed April 2022.
5. Jascholt I, Lai O, Zillikens D et al. Periodontitis in oral pemphigus and pemphigoid: A systematic review of published studies. *Journal of the American Academy of Dermatology.* 2017;76(5):E3. Accessed April 2022.
6. Langan SM, Smeeth L, Hubbard R et al. Bullous pemphigoid and pemphigus vulgaris-incidence and mortality in the UK: population based cohort study. *The BMJ.* 2008;337(7662):a180.
7. Office for National Statistics. Number of deaths from bullous pemphigoid and pemphigus vulgaris by 5 year age group in England and Wales, 2001 to 2014. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/adhocs/005442numberofdeathsfrombullouspemphigoidandpemphigusvulgarisby5yearagegroupinenglandandwales2001to2014. Accessed April 2022.
8. European Medicines Agency. Assessment Report: MabThera®. Procedure No.: EMEA/H/C000165 - II/0150. Jan 2019. Available at: https://www.ema.europa.eu/documents/variation-report/mabthera-h-c-165-ii-0168-epar-assessment-report-variation_en.pdf. Accessed April 2022.
9. Roche Products Limited. MabThera 500 mg concentrate for solution for infusion. Summary of Product Characteristics. October 2021. Available at: https://www.medicines.org.uk/emc/product/793/smpc. Accessed April 2022.
10. Sandoz Limited. Rixathon®. Summary of Product Characteristics. Apr 2021. Available at: https://www.medicines.org.uk/emc/product/2714/smpc. Accessed April 2022.
11. Pfizer Limited. Ruxience®. Summary of Product Characteristics. April 2022. Available at: https://www.medicines.org.uk/emc/product/11792/smpc. Accessed April 2022.
12. Napp Pharmaceuticals Limited. Truxima®. Summary of Product Characteristics. January 2022. Available at: https://www.medicines.org.uk/emc/product/8878/smpc. Accessed April 2022.
13. NHS England. Clinical Commissioning Policy: Rituximab for immunobullous disease. 16035/P Version 2.0. July 2021. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/06/cc-policy-rituximab-for-immonobullous-disease-ocular-v2.pdf. Accessed April 2022.
14. All Wales Therapeutics and Toxicology Centre. Rituximab One Wales Interim Decision. Ref OW10. Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/one-wales-rituximab-for-pemphigus-and-pemphigoid/. Accessed April 2022.

15. 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://awttc.nhs.wales/accessing-medicines/medicine-recommendations/rituximab-mabthera8/. Accessed April 2022.
16. Joly P, Maho-Vaillant M, Prost-Squarcioni C et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *The Lancet.* 2017;389:2031-2040.
17. Werth VP, Joly P, Mimouni D et al. Rituximab versus Mycophenolate Mofetil in Patients with Pemphigus Vulgaris. *New England Journal of Medicine.* 2021;384(24):2295-2305.
18. Lee MS, Yeh YC, Tu YK et al. Network meta-analysis-based comparison of first-line steroid-sparing adjuvants in the treatment of pemphigus vulgaris and pemphigus foliaceus. *Journal of the American Academy of Dermatology.* 2021;85(1):176-186.
19. Agarwal A, Hall RP, Bañex LL et al. Comparison of rituximab and conventional adjuvant therapy for pemphigus vulgaris: A retrospective analysis. *PLoS One.* 2018;13(9).
20. Perifani V, Dalamaga M, Theodoropoulos K et al. Real world evidence: Patients with refractory pemphigus treated with Rituximab. *Metabolism open.* 2021;12:100142.
21. Beissert S, Werfel T, Frieling U et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Archives of Dermatology.* 2006;142(11):1447-1454.
22. Heelan K, Hassan S, Bannon G et al. Cost and Resource Use of Pemphigus and Pemphigoid Disorders Pre- and Post-Rituximab. *Journal of Cutaneous Medicine and Surgery.* 2015;19(3):274-282.
23. Hébert V, Vermeulin T, Tanguy L et al. Comparison of real costs in the French healthcare system in newly diagnosed patients with pemphigus for first-line treatment with rituximab vs. standard corticosteroid regimen: data from a national multicentre trial. *Britsh journal of Dermatology.* 2020;183(1):121-127.
24. Brodszky V, Tamási B, Hajdu K et al. Disease burden of patients with pemphigus from a societal perspective. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2021;21(1):77-86.
25. Schultz B, Latour E, and Fett N. Quality of life remains poor for patients with pemphigus vulgaris despite targeted therapies. *Research letters in British Journal of Dermatology.* 2019;181(5):1101-1103.
26. Rencz F, Ruzsa G, Tamási B et al. PSS60 - UTILITY ASSESSMENT FOR PEMPHIGUS HEALTH STATES USING VISUAL ANALOGUE SCALE AND TIME TRADE-OFF METHODS. *Value in Health.* 2018;21:S433-S433.
27. Yale M, Bucci M, Boulanger V et al. Understanding real-world treatment patterns and quality of life in patients with pemphigus and pemphigoid using a patient registry database. *Value in Health.* 2019;May 2019, S347.
28. Rencz F, Gulácsi L, Tamási B et al. Health-related quality of life and its determinants in pemphigus: a systematic review and meta-analysis. *Research letters in British Journal of Dermatology.* 2015;173(4):1076-1080.
29. Heelan K, Hitzig SL, Knowles S et al. Loss of Work Productivity and Quality of Life in Patients With Autoimmune Bullous Dermatoses. *Journal of Cutaneous Medicine and Surgery.* 2015;19(6):546-554.

30. Sajedianfard S, Handjani F, Saki N et al. Family dermatology life quality index in patients with pemphigus vulgaris: A cross-sectional study. *Indian Journal of Dermatology, Venereology and Leprology.* 2021;87(3):375-378.
31. Kapre A, Werth VP, Pordeli P et al. PRO68 Patient-Reported Outcomes in Patients with Pemphigus Vulgaris Treated with Rituximab in the Phase 3 PEMPHIX Study. *Value in Health.* 2021;24:S210. Available at: https://doi.org/10.1016/j.jval.2021.04.1053. Accessed May 2022.
32. Supplement to: Werth VP, Joly P, Mimouni D et al. Rituximab versus Mycophenolate Mofetil in Patients with Pemphigus Vulgaris. *New England Journal of Medicine.* 2021;384(24):2295-2305.
33. Rashid H, Poelhekken M, Meijer JM et al. The positive impact of rituximab on the quality of life and mental health in patients with pemphigus. *JAAD International.* 2022;7:31-33.
34. Joint Formulary Committee (2022) British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Available at: http://www.medicinescomplete.com. Accessed May 2022.
35. NHS Prescription Services (2022) NHS Drug Tariff April 2022. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Accessed May 2022.
36. Martin LK, Werth V, Villanueva E et al. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev.* 2009(1):Cd006263.
37. Chams-Davatchi C, Esmaili N, Daneshpazhooh M et al. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *Journal of the American Academy of Dermatology.* 2007;57(4):622-628.
38. Sokolovska S, Varigos G, and Scardamaglia L. Outcomes of Pemphigus Treatments at the Royal Melbourne Hospital over 5 Years on Immune Suppressive Therapies used over this Time: A Retrospective Analysis. *The Journal of Clinical & Experimental Dermatology Research.* 2014;5(5).
39. Wang HH, Liu CW, Li YC et al. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Dermato-Venereologica.* 2015;95(8):928-932.
40. Amber KT, and Hertl M. An assessment of treatment history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab. *The Journal of the European Academy of Dermatology and Venereology.* 2015;29(4):777-782.
41. Currimbhoy S, Zhu V, Dominguez AR et al. Rituximab in the treatment of 38 patients with Pemphigus with long-term follow-up. *The Journal of the European Academy of Dermatology and Venereology.* 2016;30(6):1050-1052.
42. 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.
43. 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 and Leprology.* 2020;86(1):39-44.
44. Kanokrungsee S, Anuntrangsee T, Tankunakorn J et al. Rituximab Therapy for Treatment of Pemphigus in Southeast Asians. *Drug Design, Development and Therapy.* 2021;15:1677-1690.
45. Nosrati A, Mimouni T, Hodak E et al. Early rituximab treatment is associated with increased and sustained remission in pemphigus patients: A retrospective cohort of 99 patients. *Dermatologic Therapy.* 2022;35(5):e15397.

46. Tovanabutra N, Bax C E, Feng R et al. Temporal Outcomes after Rituximab Therapy for Pemphigus Vulgaris. *Journal of Investigative Dermatology.* 2022;142(4):1058-1064.

Appendix 1. Overall results of relevant publications of rituximab to treat pemphigus vulgaris

Reference	Study details	Main results
Sokolovska et al. (2014)[38]	This study was used to identify whether quality of life had improved in response to treatments administered for patients with biopsy proven PV at the Royal Melbourne Hospital Department of Dermatology over a 5-year period. This was evaluated using the PDAI and ABSIS scoring systems. Secondary outcomes included any outlying adverse treatment outcomes additional to the common treatments adversely affecting quality of life.	With the exception of two severe PV cases, all patients have their treatments documented as significantly improving their overall quality of life. The mean "most recent" PDAI score was 7.333, which was significantly lower than the mean pre-treatment PDAI of 47.762. The most recent ABSIS score had a mean value of 6.952, which was also markedly lower than the mean pre- treatment ABSIS score of 63.6976. There was significant morbidity and consequent quality of life impairment in response to azathioprine and systemic prednisolone in particular. Treatment of PV with rituximab infusions appeared to significantly improve quality of life within the cohort of this study, provided it was used in refractory cases of PV that were resistant to other immunosuppressive therapies.
Wang et al. (2015)[39]	This is a meta-analysis of efficacy of different dosing regimens of rituximab to treat pemphigus that included 30 studies identified by a systematic review. The studies included 26 case series, one randomised comparative study and three comparative studies. Subjects under 18 years were excluded. Patients (496 with PV) were grouped into high and low dose regimens.	Seventy-six percent of patients achieved complete remission after one cycle of rituximab. Mean time to remission was 5.8 months, with a remission duration of 14.5 months and a 40% relapse rate. The pooled estimate showed no significant differences in complete remission and relapse rates between patients treated with high-dose (near or ≥ 2,000 mg/cycle) versus low-dose (< 1,500 mg/cycle) rituximab. In the fully adjusted analysis, high-dose rituximab was associated with longer duration of complete remission compared with low-dose rituximab.
Amber & Hertl (2015)[40]	Retrospectively evaluated published case reports of 155 people with pemphigus (124 with PV), with ages ranging from 4 to 86 years, who were treated with a single cycle of rituximab.	Complete remission, defined as the absence of new and/or established lesions for at least 2 months, was achieved by 80% of patients. No associations were identified between clinical outcome and age, number of previous treatments, and use of adjuvant medicines.

Reference	Study details	Main results
Currimbhoy et al. (2015)[41]	This is a retrospective review of 38 eligible patients aged 19–77 years with pemphigus (30 with PV) 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. If complete remission was not achieved, rituximab 500 mg every 6 months was given until complete remission.	The mean follow-up period was 27 months (±16 months). After the first cycle of rituximab 68% of all 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.
Tavakolpour et al. (2018)[42]	This systematic review gives qualitative assessment of the sixteen-year history of rituximab therapy for the treatment of pemphigus vulgaris. The review included 1,085 patients with conditions, including unresponsive childhood/juvenile or adult PV patients, women of childbearing age, those with chronic infections with the risk of reactivation.	The authors concluded that overall, rituximab seems a very potent treatment for refractory PV patients, who do not respond well to other treatments. Although the majority of PV patients usually achieve remission within a maximum of six months, due to unknown reasons, delayed effects of rituximab can cause complexity of the disease. For those cases, additional courses of rituximab could be recommended.
De et al. (2020)[43]	This retrospective review of 146 pemphigus patients (130 with PV) to assess the proportion of patients achieving complete remission off treatment, time to achieve complete remission off treatment, proportion of patients who relapsed after achieving complete remission off treatment, time taken to relapse, duration and total cumulative dose of corticosteroids administered after rituximab.	Pooled results of all patients included CRoff therapy 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 CRoff therapy for a mean of 9.1 months.
Kanokrungsee et al. (2021)[44]	This retrospective, single-centre, cohort study included 39 patients diagnosed with PV that were treated with rituximab at a hospital in Thailand.	Complete remission (no new and/or established lesions for at least 2 months) was achieved by 31 patients with PV (79.5%) on therapy over a median time of 6.36 months; 14

Reference	Study details	Main results
	Patients received either four weekly infusions of 375 mg/m^2 rituximab or 1,000 mg two weeks apart.	patients (35.9%) achieved complete remission off therapy. Ten patients (32.3%) relapsed after a median duration of 14 months.
Rashid et al. (2022)[33]	A single centre observational study that included 47 patients with pemphigus (29 with PV) treated with rituximab. Two infusions of 1000 mg of rituximab were administered within an interval of 2 weeks, followed by 500 mg at months 6 and 12. Patient reported outcome measurements were collected, including the following: DLQI, visual analog scale in pain, HADS, and TABQOL.	This study showed the positive effect of rituximab on patients' well-being, QOL, and treatment-specific QOL during rituximab treatment. The improvement in DLQI and TABQOL was observed after 6 and 12 months, proving the short term and long-term effects of the first 2 infusions. Both DLQI and TABQOL showed a decrease among month 0, month 0.5, month 6, and month 12 ($n = 47$, $p < 0.001$ and $p = < 0.001$, respectively). For both, the decrease was most pronounced between month 0 and month 6 (DLQI, -100%, $p < 0.001$; TABQOL, -36.4%, $p < 0.001$) and between month 0 and month 12 (DLQI, -100%, $P < 0.001$; TABQOL, -45.4%, $p = 0.002$). The observed decline in the anxiety scores during treatment may contribute to the positive effect of rituximab. Contrarily, no improvement in depression was observed, possibly because it is a result of a combination of long-term non-disease-related factors and disease burden.
Nosrati et al. (2022)[45]	This retrospective, single-centre, cohort study included 99 pemphigus patients (85 with PV) treated with rituximab to assess factors associated with disease remission and early relapse following the first rituximab cycle. Two infusions of 1000 mg of rituximab were administered within an interval of 2 weeks and patients were followed up for a minimum of 12 months following the first rituximab cycle.	Median follow-up after the first rituximab cycle was 37 months (range 12–155). After a single rituximab cycle, 64 PV patients (75.3%) achieved remission. Increased time to rituximab was associated with decreased remission rates (OR, 0.98 per month; 95% CI, 0.97–0.998). Of patients in remission with sufficient follow-up, 12 PV patients (20%) experienced an early relapse (≤12 months from remission). Prolonged time to rituximab and increased baseline disease severity, were associated with early relapse (OR, 1.02 per

Reference	Study details	Main results
		month; 95% CI, 1.001–1.04; OR, 1.04 per point; 95% CI, 1.01–1.08, accordingly).
Tovanabutra et al. (2022)[46]	Patients with PV were followed for at least 12 months after first rituximab cycle (RTX1) (n = 107) and second rituximab cycle (RTX2) (n = 63). Dosing was either 1,000 mg on days 1 and 15 or 375 mg/m^2 weekly for 4 weeks based on physician discretion. The primary clinical outcome, selected before case review, was CROT; the secondary outcome was CR, either on minimal therapy or CROT.	The maximal prevalence of the first CROT after a single cycle of rituximab was 32.4%, occurring 12 months after RTX1. Additional rituximab cycles led to a 12-month CROT rate of 38.1% and maximal CROT prevalence of 43.1% 36 months after RTX1. These results are consistent with the 12-month CR prevalence of 40.3% reported in the PEMPHIX study. The cumulative probability of relapse was 61.5% and 51.5%, occurring at a median duration of 18.3 months and 19.9 months, respectively, after achieving CROT after RTX1 or RTX2, respectively. Similarly, 65.6% and 59.5% of patients who achieved CR after RTX1 and RTX2, respectively, experienced disease relapse after a median duration of 18.3 months and 18.8 months, respectively.
CI: confidence ratio; CRoff complete remission off prednisone therapy; CROT: complete remission off oral systemic therapy; DQLI: Dermatology Quality of Life Index (lower scores show better outcomes); HADS: Hospital Anxiety and Depression Scale: MMP: mucous membrane pemphigoid; OR: odds ratio; PF: pemphigus foliaceus; SUCRA: Surface Under the Cumulative Ranking; TABQOL: Treatment of Autoimmune Bullous Disease Quality of Life		