Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

One Wales Medicines Assessment Group Recommendation
Rituximab. Concentrate for solution for infusion (OW13)

Date of advice: August 2019
Date of last review: June 2026
AWTTC reference number: OW13

Using the agreed starting and stopping criteria, rituximab can be made available within NHS Wales for the second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia in patients where other health technology appraisal-approved regimens are unsuitable.

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

The risks and benefits of the off-label use of rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

This recommendation has been endorsed by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

This advice has been reviewed four times by OWMAG since its issue in 2019 with no new evidence identified to affect the current recommendation. Therefore, this advice will no longer undergo review by OWMAG unless new evidence becomes available.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions.

One Wales advice assists consistency of access across NHS Wales.

Starting and stopping criteria for rituximab as second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia

Start criteria:
Rituximab may be commenced after evidence of progression on azathioprine and/or mycophenolate mofetil and nintedanib, in line with current National Institute for Health and Care Excellence (NICE) recommendations.[1] For some patients nintedanib may be used as adjunctive treatment with rituximab. A request for rituximab should be made following regional interstitial lung disease multi-disciplinary team diagnosis review and treatment recommendation. Rituximab is recommended only in circumstances where other health technology appraisal-approved regimens are unsuitable or treatment has failed.

Progression is defined as:

- 10% decline percent predicted forced vital capacity (FVC) on first- or second-line therapy within 12 months; or
- 15% decline percent predicted transfer factor for carbon monoxide (TLCO) on first- or second-line therapy within 12 months; or
- significant radiological evidence of progression whilst on first- or second-line therapy within 12 months.

Patients who satisfy the start criteria will be prescribed rituximab after consultation with the patient and/or carer considering potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The recommended rituximab treatment dose regimen is 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. A further 1 g may be offered within the first 12 months and then annually, according to response.

Monitoring:

- Pulmonary function tests every 4–6 months.
- Repeat high resolution CT scan in event of physiological decline

Stop criteria:
Treatment with rituximab should be discontinued according to one or more of the following definitions of disease progression:

- 10% decline percent predicted FVC on rituximab therapy within 12 months; or

- 15% decline percent predicted TLCO on rituximab therapy within 12 months; or
- significant radiological evidence of progression whilst on rituximab therapy within 12 months.

1. National Institute for Health and Care Excellence. Nintedanib for treating progressive fibrosing interstitial lung diseases (TA747). Nov 2021. Available at: https://www.nice.org.uk/guidance/ta747. Accessed Dec 2023.

This report was prepared by the All Wales Therapeutics and Toxicology Centre in March 2026. It summarises any new evidence available since the last review in November 2023 and patient outcome data collected in the past two years.

Background: Interstitial lung diseases are a heterogeneous group of disorders that cause scarring of the lungs. The scarring causes stiffness in the lungs which makes it difficult to breathe. A small number of people in Wales have interstitial lung disease associated with a connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia that does not respond to treatment with conventional oral immunosuppressants. Connective tissue diseases include scleroderma and rheumatoid arthritis. Progressive fibrotic interstitial lung disease is also a significant aspect of anti-synthetase syndrome.

In 2017, NHS England reviewed and concluded not to routinely commission rituximab to treat connective tissue disease-associated interstitial lung disease. Clinicians in Wales considered there to be an unmet need in NHS Wales and identified a cohort of patients who could benefit from rituximab treatment. Based on this unmet need, rituximab was considered suitable for assessment through the One Wales process. The NHS England decision has not changed since 2017.

In November 2021, the National Institute for Health and Care Excellence (NICE) recommended nintedanib (Ofev®; TA 747) to treat progressive fibrosing interstitial lung diseases. A clinical expert in Wales has indicated that although nintedanib is now an option for this patient group, rituximab remains an option for those patients with a predominately inflammatory phenotype where other immunosuppressants are unsuitable. This place in pathway is reflected in the current start/stop criteria.

This is the fourth review of the evidence supporting the One Wales decision (OW13). If this review finds that the latest evidence still supports the decision, we propose that this decision is added to a static list and will not be routinely reviewed.

Current One Wales Decision: recommended as a second or third-line treatment option.

Licence status: off-label use for this licensed medicine

Guidelines: Since the last review of this decision in 2023, the European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of systemic sclerosis have been published in full (Del Galdo et al., 2025). EULAR recommends that the use of rituximab (or mycophenolate mofetil or cyclophosphamide) should be considered to treat systemic sclerosis-associated interstitial lung disease. These recommendations were considered substantially new by EULAR, compared to the 2017 iteration of the guideline. The level of evidence for these recommendations was 1a and the strength of the recommendations was rated A, indicating that the evidence is strong.

Licensed alternative medicines or Health Technology Assessment (HTA) advice for alternative medicines: No new medicines or HTA advice reported for this indication.

Effectiveness: AWTTC conducted a literature search to identify new evidence since the previous external review in 2023. We excluded: any studies published before 2024; conference abstracts; case series and case reports; non-English papers; any systematic reviews in which all the included studies were also included in other systematic reviews; studies conducted in patients in regions outside Europe; and studies in which the dose of rituximab used differed from the dose recommended in the One Wales decision (where reported). Our literature search identified six systematic reviews and three studies, including a cost-effectiveness study based on results from the RECITAL trial, mentioned in our last review in 2023. The other two studies were: a retrospective study and a study using real-world evidence from a European registry.

The cost-effectiveness study is discussed below. The systematic reviews and other studies are summarised in the Appendix; including information on the comparators used and the effect size of the primary outcome. It was not always clear if the use of rituximab was second-line or later in the studies, in line with the current One Wales decision.

Studies assessed improvements in lung function by measuring changes in forced vital capacity (FVC), the total volume of air that can be exhaled forcefully after taking a deep breath, and changes in the diffusing capacity of the lungs for carbon monoxide (DLCO), which measures how efficiently the lungs transfer carbon monoxide from inhaled air into your bloodstream.

The largest systematic review and meta-analysis (Zhang et al., 2025) studied rituximab to treat connective tissue disease-associated interstitial

lung disease (CTD-ILD) and included 40 studies. Results showed that rituximab significantly improved forced vital capacity (expressed as a percentage of the predicted value, FVC% [$P < 0.05$]) and diffusing capacity of the lungs for carbon monoxide (expressed as a percentage of the predicted value, DLCO% [$p < 0.01$]) compared with the control group who did not receive rituximab.

Two systematic reviews and meta-analyses studied treatments of systemic sclerosis-associated interstitial lung disease (SSc-ILD) (Anwar et al., 2025 and Wu et al., 2025) and each included two studies that evaluated rituximab. Wu et al. concluded that rituximab and tocilizumab might be the optimal treatments for SSc-ILD. Tocilizumab ranked highest (surface under the cumulative ranking probability [SUCRA] 0.904) in slowing the deterioration of FVC, followed by rituximab (0.709); rituximab ranked highest in improving DLCO (0.842) followed by mycophenolate mofetil (0.566). In the review by Anwar et al., network analysis comparing cyclophosphamide with placebo and other immunosuppressants seemed to favour cyclophosphamide over rituximab. The analysis showed potential heterogeneity between the included studies ($I^2 = 0.81$), which suggested that the meta-analysis was not robust.

Two systematic reviews were conducted on treatments for rheumatoid arthritis-associated interstitial lung disease (RA-ILD) (Ines et al., 2025 and Fassio et al., 2025). In the review by Ines et al., 2025, meta-analysis concluded that rituximab was effective in managing RA-ILD: stabilisation or improvement of lung function was seen in more than half of the patient cohorts across all studies (proportion of stabilisation ranged from: 42% to 100% based on pulmonary function tests; 42% to 87.5% by high-resolution computed tomography). The review also concluded that rituximab had an overall acceptable safety profile. In the review by Fassio et al., 2025, meta-analysis supported rituximab, abatacept and nintedanib as promising treatment options for RA-ILD. Pooled pre-post %FVC estimates were associated with stabilisation or improvement for rituximab and meta-analyses showed no significant differences in %DLCO changes with rituximab compared to non-users of rituximab.

A systematic review by Kouranloo et al., 2025 of treatments for anti-synthetase syndrome-associated interstitial lung disease (ASS-ILD), which included rituximab, showed that improvements in FVC and DLCO of 12.2% and 2.9% respectively were seen with rituximab treatment.

Multigroup comparison using data from a large European Scleroderma Trials and Research (EUSTAR) registry, which included 172 SSc-ILD patients given rituximab, showed comparable efficacy, in terms of the primary outcome (FVC percent predicted), between rituximab, tocilizumab, mycophenolate mofetil and cyclophosphamide (p = 0.101 [Yan et al., 2025]). Data from a retrospective study showed that rituximab given together with mycophenolate mofetil significantly increased FVC more than rituximab alone (p = 0.003 [Barde et al., 2025]).

Safety: No new safety concerns with rituximab were identified.

Cost-effectiveness: In our previous review of this One Wales decision in 2023, we reported results from the RECITAL study, a double-blind, double-dummy phase IIb randomised controlled trial of rituximab versus cyclophosphamide to treat CTD-ILD conducted in the UK. In 2024, the final research report of the RECITAL study (Maher et al., 2024) was published and included a cost-effectiveness analysis. This is the first relevant cost effectiveness analysis AWTTC has identified for this medicine and indication. The analysis concluded that, based on the results of the RECITAL trial and from a UK healthcare payer perspective, rituximab was more cost effective than cyclophosphamide as a treatment for severe or progressive CTD-ILD.

The cost-effectiveness analysis used costs estimated from the NHS perspective; only direct medical costs were accounted for. Quality-adjusted life-years (QALY) were derived from utility values (EuroQoL-5 dimensions 5-levels; EQ-5D-5L) taken from the RECITAL trial, collected at 24 weeks and 48 weeks.

The primary outcome was cost-effectiveness, defined by costs in GB pounds, QALYs, incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (INMB). A strategy was considered cost effective if it was: more effective and less costly (dominant strategy); or more effective and more expensive with an ICER below £30,000.

Key assumptions made in the cost-effectiveness model were:

- the total cost of adverse events was only for moderate or severe adverse events (grade 3 or grade 4) and that all hospitalisations to treat adverse events were non-elective short stay (day case);
- the main treatment options reported in the RECITAL trial diary were included as alternatives to treat the reported adverse events;
- that adverse events occurred once;

- cyclophosphamide dosage was calculated assuming a body weight of 70 kg;
- one-way sensitivity analysis was carried out assuming a 10% increase or decrease in input parameters.

The analysis showed that after 12 months, rituximab was a dominant strategy over cyclophosphamide, generating a cost saving of £1,110.99 and a gain in quality of life of 0.022 QALYs per patient. Rituximab provided an incremental monetary benefit compared with cyclophosphamide. In probabilistic sensitivity analyses rituximab was cost-effective in 81.4% of 1,000 simulations, and cyclophosphamide was cost-effective in 18.6% of the simulations, assuming a willingness to pay limit of £30,000. One-way sensitivity analysis showed that the main drivers that influenced the ICER values were outpatient costs and treatment of adverse events in the cyclophosphamide group, alongside the rituximab cost.

Although the drug costs for rituximab treatment were higher than the costs for cyclophosphamide (UK costs), the economic analysis suggested that, when considering the patterns of healthcare interaction undertaken by participants in the RECITAL trial, rituximab is the dominant strategy. Rituximab continued to be cost effective under less favourable assumptions, where parameters with the highest level of uncertainty were varied, assuming a willingness-to-pay limit of £30,000. Rituximab would become not cost-effective compared to cyclophosphamide if the price increased by 5%.

Since the RECITAL trial was started, the patent for rituximab expired, and several cheaper biosimilar versions are available in the UK. The reduced costs of these biosimilar alternatives further enhance the cost of rituximab compared to cyclophosphamide. The cost-effectiveness analysis suggests that using rituximab to treat connective tissue disorder-interstitial lung disease is potentially cost-saving compared to cyclophosphamide.

Budget impact: Nineteen patients in South East Wales have received treatment with rituximab in the 2 years since the last review. Extrapolating these figures for the whole of Wales provides an estimate of approximately 29 patients treated annually. This is slightly higher than the original estimate of 20 patients per year and higher than numbers reported in previous reviews. In the first 2 years following the decision uptake was lower than expected; most likely due to the COVID-19

pandemic. No further information has been provided on which to assess the budget impact.

Impact on health and social care services: Minimal.
Patient outcome data: In the two years since the last review nine patients in Cardiff and Vale UHB have received treatment with rituximab for ILD. [confidential information removed]. In Aneurin Bevan UHB ten patients have received treatment in the past two years, no further outcome information has been provided.

Next review date: This advice has been reviewed four times by OWMAG since its issue in 2019 with no new evidence identified to affect the current recommendation. Therefore, this advice will no longer undergo review by OWMAG unless new evidence becomes available.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

References: a full reference list is available on request.

Appendix: Summary of relevant stu` dies identified

Reference	Study details	Main results
Systematic reviews		
CTD-ILD		
Zhang et al., 2025	A systematic review and meta-analysis of the efficacy of RTX to treat CTD-ILD. 40 studies included, involving 1052 patients. 14 studies reported the administration method of RTX as 1,000 mg administered twice with a two-week interval (p = 0.25), two studies administered 375 mg/m^2 once a week, a total of four times (p = 0.06), 21 studies did not report dosing information (p < 0.01). Changes in FVC% (40 studies) and DLCO% (36 studies) before and after RTX use were compared and analysed between RTX and control groups.	RTX significantly improved FVC% (WMD = 7.1, 95% CI = 4.58 to 9.62; p < 0.05) and DLCO% (WMD = 5.26, 95% CI= 2.86 to 7.65; p < 0.01), and reduced the mRSS (WMD = −6.58, 95% CI = −8.27 to −4.89; p < 0.01) and prednisone dose (WMD = −6.94, 95% CI = −11.96 to −1.92; p < 0.01). Among RTX-treated patients: 30.3% improved (25 studies; 95% CI = 22.0% to 39.3%); 45.3% remained stable (23 studies; 95% CI = 35.1% to 55.6%) and 10% progressed (26 studies; 95% CI = 5.7% to 15.1%). Pooled mortality from 30 studies was 5% (95% CI = 2.3% to 8.4%). The pooled hospitalisation rate from 16 studies was 6.7% (95% CI = 1.4% to 14.3%), and data from 16 studies showed a pooled infection rate of 22.4% (95% CI = 13.4% to 32.7%).
SSc-ILD		
Anwar et al., 2025	A meta-analysis and network meta-analysis of the effectiveness of CYC to treat SSc-ILD compared with placebo and other immunosuppressants including RTX. Eight studies included (four RCTs and four observational studies) involving 484 patients.	A mild but statistically insignificant difference was observed in FVC between CYC and RTX, yet the analysis leaned toward favouring CYC (overall [Cohen's d standard, −0.31; standard error, 0.19; 95% CI = −0.68 to 0.05; p = 0.09]). Network meta-analysis showed RTX had the lowest FVC outcome p score (0.3410), indicating a lesser

Reference	Study details	Main results
	57 patients (in 2 studies) were treated with two doses of IV RTX two weeks apart (doses ranged from 500–1000 mg). The review evaluated a range of lung function parameters. The difference in FVC between the CYC and RTX groups was reported.	impact on FVC outcomes compared to other treatments. However, variation in the CIs and weights for the fixed effects model versus the random effects model showed potential heterogeneity between the studies (I^2 = 0.81) and suggests that the meta-analysis was not robust. The study concluded that the findings do not decisively support the superiority of CYC over other treatments for most SSc-ILD lung function parameters.
Wu et al., 2025	A systematic review and meta-analysis evaluating the clinical effectiveness and safety of six treatments for SSc-ILD, including RTX. Eight randomised controlled trials, involving 1195 patients, were included. Two studies evaluating RTX were included; one at a dose of 375 mg/m^2 per week for four weeks (IV); one at a dose of 1,000 mg on Day 0 and Day 15 (IV). Outcomes included FVC% predicted, DLCO% predicted, and serious adverse events.	The study reported no significant statistical differences in efficacy and safety between the six treatments. However, in slowing the deterioration of FVC, TCZ (0.904) and RTX (0.709) ranked the highest in SUCRA (i.e. better-performing relative to other evaluated treatments). In improving DLCO, RTX (0.842) and MMF (0.566) ranked the highest. RTX showed the lowest probability for SAEs with a SUCRA ranking of 0.591. One patient died of severe pulmonary hypertension after 5 months of RTX treatment, which may be related to the disease process. One patient developed severe hypoalbuminemia, which led to the discontinuation of treatment. The study concluded that RTX and TCZ may be the optimal interventions for SSc-ILD.
ASS-ILD		

Reference	Study details	Main results
Kouranloo et al., 2025	A systematic review of the management and treatment outcomes for ASS-ILD. Ten studies were included (nine cohort studies and one case series) involving 514 patients. 88 patients received RTX (two infusions of 1 g of RTX on Day 1 and Day 15, or a dose of 375 mg/m^2 once weekly for four weeks). The review evaluated PFTs including FVC and DLCO. Where possible, meta-analysis using a random effects model was conducted for outcomes of PFTs.	Due to heterogeneity of methodology and cohorts, direct comparison was not possible for most drugs. Patients receiving RTX had an overall mean 12.2% improvement in FVC from baseline and a 2.9% increase in DLCO at one year. The review reported that two patients who receiving RTX died post-treatment due to *Pneumocystis jirovecii* infection. The review concluded that no conclusive difference between effectiveness of treatments was identified.
RA-ILD		
Ines et al., 2025	A systematic review and meta-analysis to study the efficacy and safety of RTX to treat RA-ILD. 20 studies were included, involving 1,619 patients who were given RTX. RTX dosage data were available in nine of the 20 studies; all these studies used the same regimen: RTX infusion of 1 g of RTX given on Day 1 and Day 15. Five studies reported that RTX infusions were preceded by pre-medication with 100 mg of methylprednisolone. PFTs were the most used evaluation method, followed by HRCT. Two studies reported survival and mortality rates.	Stabilisation or improvement of lung function was seen in more than half of the patient cohorts across all studies (42% to 100% based on PFTs; 42% to 87.5% by HRCT). All included studies concluded that RTX was effective in the management of RA-ILD, reducing the risk of progression. Meta-analysis results showed that the proportion of patients showing disease progression was 14.5% (95% CI=7.6% to 25.8%) (95% PI = 2% to 69%) based on PFTs; and 19.5% (95% CI = 8.1 to 40%) (95% PI = 1 to 84%) based on HRCT. An overall acceptable safety profile was noted, with respiratory-related mortality ranging from 4% to 14%. The most frequent adverse events were infections, with hospitalisation rates reaching approximately 21%.

Reference	Study details	Main results
Fassio et al., 2025	A systematic review and meta-analysis of studies evaluating pharmacological interventions for RA-ILD. 69 studies were included, involving 7879 patients. A total of 16 studies evaluating RTX in patients with RA-ILD were included. The review evaluated PFTs including differences in %FVC and %DLCO, risk of RA-ILD progression, severe adverse events, and mortality.	Pooled pre-post %FVC estimates were associated with stabilisation or improvement for most drugs, including RTX. Meta-analyses for RTX showed no significant differences in %DLCO changes compared to non-users of RTX. For RTX, a sensitivity analysis showed that, while the direction of the effect for %DLCO remained consistently positive across all iterations, statistical significance was observed when two studies were excluded, suggesting limited robustness of the pooled effect. Between study heterogeneity was high in all scenarios. The study concluded that ABA, RTX, and nintedanib appear to be promising treatment options for RA-ILD.
Clinical studies and retrospective studies		
SSc-ILD		
Barde et al., 2025	A French retrospective study of the efficacy and safety of MMF + RTX combination therapy compared with each drug given alone to treat SSc-ILD. Patients were treated with MMF + RTX, RTX or MMF or ≥12 months. 47 patients received MMF + RTX, 30 patients received only RTX and 50 patients received only MMF. 81% of all patients and 67% of the RTX only group had ILD involvement.	Results showed mRSS remained unchanged in the RTX group (8 [2–17] at baseline, to 8 [2–15] at 12 months, p = 0.3). FVC increased significantly only in the group that received RTX + MMF. Results from 23 patients in the RTX alone group showed increased FVC at 12 months but the change was not significant (64.5 [54.5–75.5] at baseline, to 68.0 [53.0–77.0] at 12 months; p = 0.8). After excluding cross-over patients, adverse events were more frequent in the combination group (n = 12; 44.4%) than in the RTX alone group (n = 4;

Reference	Study details	Main results
	Primary outcomes were changes in mRSS and predicted FVC from baseline to 12 months. In the RTX only group, RTX was given as two 1,000 mg doses 15 days apart for 27 patients, and as 375 mg/m^2 weekly for four weeks in three patients. 21 patients and 20 patients had a maintenance RTX dose at 6 and 12 months, respectively. All patients received premedication with methylprednisolone before RTX infusion.	22.2%) or MMF group (n = 6; 28.6%), including infections (n = 10, 37% versus n = 1, 5.6%, and n = 6, 28.6%). However, the differences were not statistically significant.
Yan et al., 2025	Data from a large European Scleroderma Trials and Research (EUSTAR) registry were used to compare the effectiveness of four treatments for SSc-ILD. Data analysed were from 955 patients from 103 centres and 997 treatment observations, and included 172 patients (17.3%) in the RTX group, 96 patients (9.6%) for TCZ, 511 (51.3%) for MMF, and 218 (21.9%) for CYC. The primary endpoint was the change in FVC percentage predicted from baseline to the follow-up visit closest to one year.	The median follow-up time was 11 months (IQR: 8-14 months). After inverse probability of treatment weighting (IPTW) the mean adjusted change in FVC percentage predicted from baseline to follow-up was not significantly different by multiple group comparison (p = 0.101). Paired comparisons showed no significant difference. It was concluded that TCZ, RTX, MMF and CYC showed comparable effectiveness in treating SSc-ILD. In some subanalyses, CYC showed clinically marginal but statistically significantly better effectiveness, mainly versus TCZ.

ABA: abatacept; ASS-ILD: anti-synthetase syndrome-associated interstitial lung disease; CI: confidence interval; CTD: connective tissue disease; CTD-ILD: connective tissue disease-associated interstitial lung disease; CYC: cyclophosphamide; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IQR: interquartile range; IV: intravenous; MMF: mycophenolate mofetil; mRSS: modified Rodnan skin score; PFT: pulmonary function test; PI: prediction interval; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; RCT: randomised controlled trial; RTX: rituximab; SAE: severe adverse events; SSc-ILD: systemic sclerosis-associated interstitial lung disease; SUCRA: surface under the cumulative ranking probability; TCZ: tocilizumab; WMD: weighted mean difference

AWTTC

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