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

One Wales Medicines Assessment Group Recommendation
Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas (OW08)

Date of advice: 27 March 2017
Date of last review: 22 April 2026
AWTTC reference number: OW08

Bendamustine in combination with rituximab can be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia under the following circumstances:

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.

- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.

- For the treatment of Waldenstrom's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

The risks and benefits of the off-label use of bendamustine and 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 7 times by OWMAG since its issue in 2017 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.

Seventh Review of One Wales Decision – January 2026

OW08: Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas.

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

Background: Bendamustine with rituximab is available in NHS England through clinical commissioning for the first line treatment of advanced, indolent non-Hodgkin's lymphoma. Bendamustine is available through NHS England's Cancer Drugs Fund (BEN6) for use in relapsed low-grade lymphoma, in people for whom standard treatment is unsuitable. According to the NHS England Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication.

A cohort of patients identified through data from individual patient funding request panels, and clinicians in Wales, have confirmed there to be an unmet need within the service. This cohort includes young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenström's macroglobulinaemia for whom standard therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process. Clinical experts consulted for this review supported the ongoing need for the option for use in NHS Wales for this cohort of patients.

Current One Wales Decision: Supported with restrictions.

Licence status: Off-label use for this licensed medicine combination.

Guidelines: Two new guidelines have been published since the past review. Lymphoma Study Association (LYSA) guidelines (2025) have been published for Waldenström's macroglobulinemia (WM) recommending bendamustine and rituximab (BR) in combination for the management of newly diagnosed WM in fit patients with no TP53abn mutation. BR is also recommended for relapsed or refractory WM after first-line therapy for patients with contraindications to covalent Bruton's tyrosine kinase inhibitors (cBTKi). Although no prospective studies directly compare the efficacy of different chemoimmunotherapy regimens, evidence supports BR regimen as producing the most profound responses, with the longest progression-free survival (PFS) and time-to-next-treatment. The guidelines also note that this regimen has been found to facilitate rapid disease control in highly symptomatic patients or those with large tumour masses.

British Society of Haematology guidelines (2023) have been published for the diagnosis and management of marginal zone lymphomas. These guidelines state that BR is effective for advanced stages of marginal zone lymphoma subtypes including extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue, nodal marginal zone lymphoma and splenic marginal zone lymphoma. The guidelines also state that BR may be more toxic than other chemoimmunotherapy regimens.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines:

NICE TA892: mosunetuzumab (Lunsumio®) is not recommended for the treatment of adults with relapsed or refractory follicular lymphoma who have had two or more systemic therapies, May 2023

NICE TA1001: zanubrutinib (Brukinsa®) is recommended for the treatment of adults with marginal zone lymphoma after anti-CD20-based treatment, September 2024.

NICE TA1139: epcoritamab (Epkinly®) is recommended for treating relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment, March 2026.

NICE ID3726: the appraisal of odronextamab (Ordspono®) for the treatment of relapsed or refractory follicular lymphoma (FL) in adults is awaiting development.

Effectiveness: A literature search conducted by AWTTC identified one systematic review and eight studies published after this review that are relevant to the indicated recommendation. The studies are summarised in Appendix 1, results are in line with those reported in previous studies. As in previous reports, the three comparative studies demonstrate similar or improved outcomes for BR compared to rituximab with chemotherapy (including R-CHOP).

Ou et al (2023) published a systemic review and meta-analysis of BR versus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) for patients with indolent lymphoma. The six studies included in the final analysis have already been described in previous AWTTC external reviews (Rummel et al [2013], Flinn et al [2019], Cheah et al [2016], Olszewski et al (2020), Pouyiourou et al [2020] and Mondello et al [2016]). The overall conclusion of the meta-analysis was that the BR regimen had a better potential of prolonging PFS compared to R-CHOP (HR 0.67, 95% CI 0.46 to 0.97). Comparison of adverse event rates showed infection rates to be comparable between BR and R-CHOP (relative risk [RR] 0.75, 95% CI 0.52 to 1.08, p = 0.12). The risk of grade 3 and 4 hematologic toxicities seemed to be significantly lower with BR than with R-CHOP (RR range 0.38 to 0.62).

Quality of life data was reported for one of the studies included in the analysis (Flinn et al [2019)]). Patients treated with BR reported improvements in cognitive, physical, social, and emotional functioning, and global health status as well as a reduction in dyspnoea, constipation, and fatigue at least one-timepoint. Patients treated with R-CHOP reported less nausea or vomiting after 3 treatment cycles. Six cost effectiveness studies were reported in the analysis, all of which concluded that BR was a cost-effective alternative to R-CHOP, none of the studies were from a UK perspective and have therefore limited relevance to this review (Coyle, et al [2016], Dewilde et al [2014], Sabater et al [2016], Shoji et al [2019], Zhou et al [2017], Wehler et al [2015]).

Safety: No safety evidence was identified that was not in concordance with the well-known safety profiles of bendamustine and rituximab for this indication.

Cost-effectiveness: No cost-effectiveness analyses relevant to this review were identified in this literature search.

Budget impact: In the two years since the last review eight patients have received treatment with BR for indolent lymphomas in South East Wales. Extrapolating these figures to the population for all of Wales provides an estimate of approximately eight patients treated annually. This is considerably lower than the original estimate of 77 patients, however, this is consistent with patient numbers reported since the first review in 2018 which suggests an overestimate in the original report. In addition, there are more health technology-assessed treatment options available for indolent lymphoma since the original assessment in 2017. No further information on patient numbers has been provided on which to assess the budget impact.

Impact on health and social care services: Minimal.

Patient outcome data: Eight patients in South East Wales have received treatment with BR in the 2 years since the last review [confidential information removed] Clinicians note the limited usage of this treatment in Wales but would value its continued availability through One Wales when treatment is required.

Next review date: This advice has been reviewed 7 times by OWMAG since its issue in 2017 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.

References: a full reference list is available on request.

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.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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Appendix 1.

Supporting studies with evidence for clinical effectiveness.

Indolent lymphoma subtype	Author (Year) and Study Design	Number of patients treated	Reported outcome measures			
			ORR	PFS	OS	Other
Marginal zone lymphoma	Lee et al (2025) Multicentre, open label, phase II NCT02433795 Relapsed or progressive disease	26* (52% EMZL, 48% NMZL)	81.8% *CR: 40.7%* *PR: 40.7%*	Median 46.06 months (median FU 25 months) Estimated 2-year: 79.8% Estimated 3-year: 64.5%	Median not reached Estimated 3-year: 92.3%	
	Logothetis et al (2024) Retrospective, single centre study First-line treatment	25EMZL†	100% *CR: 60%* *PR: 40%*	Median not reached Estimated 2-year: 85.2%	Median not reached Estimated 2-year: 100%	

Indolent lymphoma subtype	Author (Year) and Study Design	Number of patients treated	Reported outcome measures			
			ORR	PFS	OS	Other
	Iannitto et al (2024) Long-term follow-up of Iannitto et al (2018), a phase II, open-label single arm study First-line treatment	56 SMZL	MRR: 91% *CR: 61%* *CRu[§]: 13%* *PR: 18%*	Five-year: 83%	Five-year: 93%	
Follicular lymphoma	Baron et al (2025) Retrospective comparison of BR vs R-CHOP in two Phase II clinical trials: (Flinn et al (2014) and Rummel et al (2013)) First line treatment	2,084 (BR or equivalent: 1475[¶] R-CHOP or equivalent: 609)	NR	NR	Median 10.5 vs 11.5 years (median FU 138 months [p = 0.163]) Five year: 78% vs 80% Ten year: 58% vs 59%	TTNTD: median 96 vs 78 months (p = 0.086) TTNTD24: 13.3% vs 18.6% (p = 0.002)
Waldenström's macroglobulinemia	Autore et al (2025) Retrospective multicentre study comparing BR vs DRC vs R-chemo[**]	331 (BR: 245 DRC:116 R-chemo: 86)	93.3% vs 79.2% vs 75% (BR vs DRC and	Estimated 4-year: 80% vs 60% vs 68%	Estimated 4-year: 86% vs 89% vs 93%	

Indolent lymphoma subtype	Author (Year) and Study Design	Number of patients treated	Reported outcome measures			
			ORR	PFS	OS	Other
	First-line treatment		BR vs R-chemo p = < 0.001)			
	Laribi et al (2024) Long-term follow-up results of Laribi et al (2019) multi centre study First-line treatment	69	NR	Five-year: 66.6%	Five-year: 80%	Five-year EFS: 62.3%
	Kim et al (2024) Retrospective study comparing BR vs RCVP First-line treatment	111 (BR: 57 RCVP: 54)	93% vs 84% (p = 0.87) MRR: 88% vs 80% (p = 0.92)	Median PFS: 60.5 vs 79 months (median FU 60.7 months [p = 0.96]) Estimated 2-year: 88% vs 81% Estimated 5-year: 48% vs 55%	Median OS was not reached for BR and was 153.4 months for RCVP (median FU 60.7 months [p = 0.37]) Estimated 2-year:	

Indolent lymphoma subtype	Author (Year) and Study Design	Number of patients treated	Reported outcome measures			
			ORR	PFS	OS	Other
					91% vs 91% Estimated 5-year: 64% vs 77%	

*Patients also received rituximab subcutaneously (1,400 mg) in cycles 2-8 on day 1 every 4 weeks, in addition to intravenous rituximab as per protocol.
†10 patients also received rituximab maintenance treatment.
§CRu: unconfirmed complete response (some degree of cytopenia and splenomegaly at the end of treatment but meet the criteria for CR at the first follow-up visit as defined by Iannitto et al (2024)
¶BR cohort also included 88 patients treated with bendamustine plus obinutuzumab (BO).
**R-chemo: other rituximab-containing regimens including chlorambucil-rituximab (Chl-R), fludarabine-cyclophosphamide-rituximab (FCR) or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone R-CHOP.

BO: bendamustine and obinutuzumab; BR: bendamustine and rituximab; CR: complete response; DRC: dexamethasone, rituximab and cyclophosphamide; EFS: event-free survival; EMZL: extranodal marginal zone lymphoma; FU: follow up; MRR: major response rate; NMZL: nodal marginal zone lymphoma; NR: not reported; ORR: objective response rate; OS: overall survival; PR: partial response; PFS: progression-free survival; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RCVP: rituximab, cyclophosphamide, vincristine, prednisone; SMZL: splenic marginal zone lymphoma; TTNTD: time-to-next-treatment or death; TTNTD24: initiation of second-line treatment within 24 months from the end of first-line treatment.