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

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

February 2024

ONE WALES INTERIM DECISION

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

Date of original advice: March 2017
Date of review: December 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

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 plus rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after two years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

This report was prepared by the All Wales Therapeutics and Toxicology Centre in October 2023. It summarises any new evidence available and patient outcome data collected since the last review in October 2022.

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 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, confirmed there to be an unmet need within the service. This cohort included: 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: No updates to guidelines since last review.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines:
NICE TA842: the appraisal of tisagenlecleucel (Kymriah®▼) for the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy was terminated due to absence of submission from the manufacturer, November 2022.

NICE TA894: axicabtagene ciloleucel (Yescarta®▼) is not recommended, within its marketing authorisation, for treating adults with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy, June 2023.

Effectiveness: A repeat literature search conducted by AWTTC identified three studies relevant to the recommendation, one focussed on indolent lymphoma and two on Waldenström's macroglobulinaemia (WM).

Suleman et al. 2023 carried out a retrospective study using linked databases comparing a real-world cohort of bendamustine/rituximab (BR; n = 2032) with a historical cohort of a combined group (n = 2032) of rituximab with either cyclophosphamide, vincristine and prednisolone (R-CVP), or cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for the first line treatment of indolent lymphoma. The results remain the same as those reported in the 2021

One Wales review as a conference abstract. The full study also reports on 5-year overall survival (OS; 80% BR versus 75% R-CVP/R-CHOP), where BR was associated with improved OS rates (hazard ratio [HR] 0.79; 95% CI: 0.69–0.91; p < 0.01). This trend was not consistent with elderly patients (> 75 years old; n = 824), for whom OS rates were comparable between treatments: 55.5% for BR (n = 401) and 55.4% for R-CVP/R-CHOP (n = 423; HR 0.97 95% CI: 0.78–1.21).

A systematic review and meta-analysis analysed the efficacy of first line treatment regimens for WM by evaluating pooled data from 11 phase II or phase III clinical trials (Chan et al. 2023). Sample size of the included studies ranged from 23 to 261. BR was associated with a higher or comparable response rate, OS and progression free survival (PFS) rate than comparators (Table 1).

Table 1. Pooled figures from 11 phase II or phase III clinical trials analysing bendamustine/rituximab in the treatment of Waldenström's macroglobulinaemia

Treatment	Response rate*	Overall survival (2 years)	Progression free survival (2 years)	Major response rate†
BR	46%	97%	89%	83%
BDRC	33%	94%	81%	85%
BBR	47%	NR	89%	89%
IR	NR	90%	82%	73%
BDR	30%	80%	69%	82%
R-CHOP	25%	NR	NR	91%
DRC	15%	91%	69%	81%
Bortezomib rituximab	8%	NR	66%	66%

BBR: bortezomib, bendamustine, rituximab; BDR: bortezomib, dexamethasone, rituximab; BDRC: bortezomib, dexamethasone, rituximab, cyclophosphamide; BR: bendamustine, rituximab; DRC: dexamethasone, rituximab, cyclophosphamide; IR: ibrutinib, rituximab; NR: not reported; R-CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone
*combining complete, near complete and very good partial response rates
†combining complete, very good partial and partial response rates

The use of BR for WM was also analysed in a multicentre, retrospective study which focused on the effect of bendamustine dose on outcomes (Arulogan et al. 2023). The results remain the same as those reported in the 2021 review as a conference abstract. As a first line treatment, those patients who received a higher bendamustine dose (≥ 1000 mg/m^2 [n = 81] compared with those receiving 800-999 mg/m^2 [n = 33]) were associated with superior major response rate (combining complete, very good partial and partial response) and PFS rate. Additionally, this trend was replicated among relapsed WM patients.

Safety: Suleman et al. (2023) analysed the toxicity of BR (n = 2032) in comparison with R-CVP/R-CHOP treatment (n = 2032). BR was associated with higher incidences of hospital admissions for infection during an initial nine-month induction period (21.9% for BR versus 17.3% for R-CVP/R-CHOP; $p < 0.01$) and during the first three years (41.2% for BR versus 33.6% for R-CVP/R-CHOP; $p < 0.01$). BR was also associated with a higher mean number of emergency department visits during the initial nine months (1.01 ± 1.68 visits for BR versus 0.85 ± 1.51 visits for R-CVP/R-CHOP; $p < 0.01$). Over a three-year period, BR patients on maintenance therapy were more likely to be admitted for infection (37.9% for BR versus 31.5% for R-CVP/R-CHOP; $p < 0.01$). For both first line and maintenance therapy BR was associated with fewer admissions for neutropenia and febrile neutropenia than R-CVP/R-CHOP.

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

Budget impact: [Confidential text removed]. This is much lower than the original numbers estimated but 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: AWTTC has been provided with data for [Confidential text removed].

Evaluation of evidence

The clinical evidence presented supports the current use of bendamustine with rituximab as a treatment option in line with the current One Wales decision. [Confidential text removed]. Bendamustine in combination with rituximab for the treatment of indolent lymphomas should only be used in circumstances where other licensed and health technology appraisal-approved regimens are unsuitable.

Next review date: 24 months

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.

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