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 mantle cell lymphoma (OW09)

## September 2021

## ONE WALES INTERIM DECISION

### Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed mantle cell lymphoma

**Date of original advice: April 2017**
**Date of review: September 2021**

**The following One Wales Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.**

Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed mantle cell lymphoma in patients currently deemed unsuitable for anthracycline-based therapy or other health technology appraisal-approved regimens.

Bendamustine in combination with rituximab is not a licensed regimen to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bendamustine with 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 12 months 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 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 assists consistency of access across NHS Wales and will be disseminated to the service following agreement of Health Board Chief Executives.**

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

**Background**
Bendamustine with rituximab is available in NHS England through clinical commissioning for the treatment of previously untreated and relapsed and refractory mantle cell lymphoma[1,2]. Although rituximab is not licensed for treating mantle cell lymphoma, the National Institute for Health and Care Excellence (NICE) mantle cell lymphoma treatment pathway recommends it in combination with chemotherapy as first-line treatment of advanced-stage mantle cell lymphoma[3].

A cohort of patients had been identified through data from individual patient funding request panels and clinicians in Wales considered there to be an unmet need within the service. This cohort includes people with untreated and relapsed mantle cell lymphoma for whom anthracycline-based therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process.

**Current One Wales Decision**
Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed mantle cell lymphoma in patients currently deemed unsuitable for anthracycline-based therapy or other health technology appraisal-approved regimens. September 2020.

**Licence status**
Bendamustine in combination with rituximab for the treatment of mantle cell lymphoma is off-label.

**Guidelines**
There have been no new relevant guidelines or updates to existing guidelines identified.

Interim NICE guidance issued in April 2020 relating to systemic anticancer treatments (NG161) during COVID-19 is still in place[4].

**Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines**
NICE ID1221: Ibrutinib for untreated mantle cell lymphoma[5]. Expected publication date: TBC. This treatment is currently on the Cancer Drugs Fund list as an interim treatment option during COVID-19 pandemic as an alternative to intravenous chemotherapy[6].

NICE TA677: Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma. Publication date: 24 February 2021[7]. This medicine is an advanced therapy medicinal product (ATMP).

**Efficacy/Effectiveness**

A repeat literature search conducted by AWTTC identified three retrospective studies.

A published conference abstract assessed the efficacy of bendamustine plus rituximab as an induction regimen for the treatment of mantle cell lymphoma (n = 97) in patients (aged 18–65 years) treated in British Columbia[8]. These patients were compared to an historical control cohort of 232 patients randomised to rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) or rituximab in combination with dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) in the European mantle cell lymphoma Younger trial. The overall response rate (ORR) was 89% (77% complete response [CR]) for bendamustine plus rituximab and 94% (54% CR) for R-CHOP/R-DHAP. The percentage of patients who proceeded to autologous stem cell transplantation (ASCT) was 77% and 78% respectively. However, 78% received maintenance rituximab (MR) in the bendamustine plus rituximab group versus only 2% in the R-CHOP/R-DHAP group. There was no statistically significant improvement for progression free survival (PFS), event free survival (EFS) or overall survival (OS) for bendamustine plus rituximab with ASCT and MR versus R-CHOP/R-DHAP with ASCT[8].

A second published conference abstract assessed overall and relative survival in relation to primary treatment of mantle cell lymphoma in 592 patients (median age 75) identified from the Swedish Lymphoma Registry[9]. Three treatment regimens were compared: bendamustine, CHOP/CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone) and the Nordic MCL2 protocol[1]. The majority of patients (562/592) also received rituximab. After adjustment for age at diagnosis, sex and diagnosis year, there was no difference in overall or relative survival between MCL2 and bendamustine plus rituximab groups. The adjusted results suggested inferior survival for patients given R-CHOP/CHOEP compared to MCL2 and bendamustine plus rituximab regimens[9].

A peer-reviewed study, using data from a Medicare database, compared treatment patterns and OS for mantle cell lymphoma patients initiating systemic treatment (n = 1,390)[10]. Bendamustine plus rituximab was the preferred frontline treatment option (35.3%) followed by ibrutinib (33.5%), rituximab alone (9.1%) and R-CHOP (6.8%). Twenty-four-month OS was 73% for bendamustine plus rituximab; 47% for ibrutinib; 72% for rituximab; and 71% for R-CHOP[10].

**Safety**

In March 2021, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update article highlighting new safety information regarding a risk of increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML) associated with the use of bendamustine[11]. The background to this safety concern refers to results from the BRIGHT and GALLIUM

[1]Cytarabine/CHOP induction with high-dose chemotherapy and autologous hematopoietic stem cell transplantation consolidation [HD-AHCT])

studies which show a higher number of cases of non-melanoma skin cancer with bendamustine containing regimens than with other treatments used for lymphoma. In the BRIGHT trial, 14 of 221 (6.3%) patients treated with bendamustine plus rituximab and 5 of 215 (2.3%) patients treated with R-CHOP/R-CVP were reported to develop squamous cell carcinoma or basal cell carcinoma. In the GALLIUM trial basal cell carcinoma was reported in 16 of 676 patients (2.4%) receiving bendamustine versus 1 of 513 patients receiving CHOP/CVP. There were also increases in the number of reports of squamous cell carcinoma in patients receiving bendamustine, while no cases were reported in patients receiving CHOP/CVP. In addition, very rare cases of PML have been reported in patients on bendamustine containing regimens. The European review of safety data also identified an increase in reporting of cases of PML when bendamustine containing therapy is used. During the period reviewed (7 January 2018 to 6 January 2020), 42 cases of PML worldwide were reported, 11 of which were fatal. This compared to 9 cases in the previous period (7 January 2017 to 6 January 2018). Although concomitant treatment was present in all cases where information was provided, a temporal relationship with bendamustine was evident in most cases. In 31 of the cases, bendamustine-containing therapy was the latest treatment before onset. The summary of product characteristics and patient information leaflet have been updated to reflect these findings[11].

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

**Budget impact**
No information on patient numbers has been received. The availability of first-line ibrutinib during the COVID-19 pandemic may have had an effect on use of this combination therapy.

**Impact on health and social care services**
The impact on the service remains minimal.

**Patient outcome data**
No patient outcome data have been provided. A clinician states that this combination continues to have a selected role in mantle cell patients.

**References**

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