AWTTC
All Wales Therapeutics & Toxicology Centre
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**Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas**

**May 2018**

## ONE WALES INTERIM COMMISSIONING DECISION

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

**Date of original advice: April 2017**
**Date of review: May 2018**

**The following Interim Pathways Commissioning Group (IPCG) 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 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.

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 General Medical Council 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 Interim Commissioning decision.

**Health board responsibility**
Health boards will take responsibility for implementing One Wales Interim Commissioning 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.**

**Background**
Bendamustine is available through NHS England's Cancer Drugs Fund for off-label use in untreated and relapsed low grade lymphoma, in people for whom standard treatment is unsuitable[1]. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication[1].

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: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenstrom'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.

**Current One Wales Interim Commissioning Decision**
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 as an alternative to rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP).
- 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. April 2017.

**Licence status**
Bendamustine in combination with rituximab for the treatment of follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia is off-label.

**Guidelines**
The National Institute for Health and Care Excellence (NICE) treatment pathway for non-Hodgkin's lymphoma was updated in March 2018 to reflect publication of new health technology appraisal advice as described below[2].

**Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines**
NICE TA513: Obinutuzumab (Gazyvaro®▼) is recommended as an option for untreated advanced follicular lymphoma in adults (first as induction treatment with chemotherapy, then alone as maintenance therapy) with a Follicular Lymphoma International Prognostic Index score of two or more, 21 March 2018[3].

NICE TA491: Ibrutinib (Imbruvica®▼) is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least one prior therapy, 22 November 2017[4].

NICE TA472: Obinutuzumab (Gazyvaro®▼) in combination with bendamustine followed by obinutuzumab maintenance is recommended for use within the Cancer Drugs Fund as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen, 30 August 2017[5].

All Wales Medicines Strategy Group: Idelalisib (Zydelig®▼) is recommended as an option for use as monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment, 3 April 2017[6].

**Efficacy/Effectiveness**

Long-term follow-up studies have been published as conference abstracts for the STiL NHL1 and BRIGHT studies[7,8]. These studies were included in the original evidence status report. STiL NHL1 was a phase III, randomised study which compared bendamustine and rituximab to rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) as first-line treatment of indolent and mantle cell lymphomas[9]. The recently published ten-year follow-up study excluded patients with mantle cell lymphoma[7]. After a median follow-up of 114 months, the time-to-next treatment was significantly prolonged in the bendamustine plus rituximab group compared to R-CHOP (hazard ratio 0.53; 95% confidence interval 0.39 to 0.70; $p < 0.001$). Overall survival was not statistically significantly different between the two treatment groups. The estimated ten-year survival rates were 71% for bendamustine plus rituximab and 66% for R-CHOP. Less second line treatments due to disease progression were needed in the bendamustine plus rituximab group (74 patients; 36%) compared to the R-CHOP group (109 patients; 56%)[7].

BRIGHT was a phase III, randomised study which compared bendamustine plus rituximab to R-CHOP or rituximab plus cyclophosphamide, vincristine and prednisone (R-CVP) as first-line treatment of indolent and mantle cell lymphomas[10]. In the recently published follow-up study, patients were monitored for at least five years to assess the effect of bendamustine plus rituximab compared to R-CHOP or R-CVP on progression-free survival, event-free survival, duration of response and overall survival[8]. Of the 447 patients enrolled in the BRIGHT study, 419 entered the five-year follow-up study. The median follow-up time was 65.0 months for the bendamustine plus rituximab group and 64.1 months for the R-CHOP/R-CVP group. The results showed that progression-free survival, event-free survival and duration of response were significantly better for the bendamustine and rituximab group compared with the R-CHOP/R-CVP group (Table 1). Similar results for progression-free survival were found in patients with indolent non-Hodgkin lymphomas (hazard ratio 0.70; 95% confidence interval 0.49 to 1.01; $p = 0.0582$). Overall survival was not statistically different between the two groups (Table 1). The safety profile was as previously reported[8].

**Table 1. Results from the BRIGHT five-year follow up study[8]**

| | Bendamustine plus rituximab | R-CHOP/R-CVP | Hazard ratio (95% CI) p value |
|---|---|---|---|
| Progression-free survival | 65.5% | 55.8% | 0.61 (0.45–0.85) p = 0.0025 |
| Overall survival | 81.7% | 85% | 1.15 (0.72–1.84) p = 0.5461 |
| Event-free survival | NR | NR | 0.63 (0.46–0.84) p = 0.0020 |
| Duration of response | NR | NR | 0.66 (0.47–0.92) p = 0.0134 |

CI: confidence interval; NR: not reported; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone.

A long-term follow-up has been published for the retrospective study (Mondello et al. 2016) included in the evidence status report. The original study was conducted in patients with low-grade non-Hodgkin's lymphoma and compared the efficacy and safety of rituximab plus bendamustine with R-CHOP[11]. The long-term follow-up study retrospectively assessed patients with follicular lymphoma grade 3A (n = 132)[12]. At a median follow-up of 15.2 years in the bendamustine plus rituximab group and 14.8 years in the R-CHOP group, the median progression-free survival was significantly longer in the bendamustine plus rituximab group compared with the R-CHOP group (15 versus 11.7 years; $p = 0.03$)[12]. This is in contrast to the original study which showed no difference in progression-free survival between both treatment groups[11].

Several conference abstracts describing the efficacy of bendamustine plus rituximab in the treatment of indolent lymphomas have been published since the One Wales decision. The data reported are consistent with those previously reported in the evidence status report. Three studies have assessed the efficacy of bendamustine plus rituximab for the treatment of Waldenstrom's macroglobulinemia. In treatment naïve and relapsed or refractory disease, high response rates and progression-free

survival rates were seen with bendamustine and rituximab treatment[13-15]. This was comparable with bortezomib, dexamethasone and rituximab, and cyclophosphamide, dexamethasone and rituximab treatments[14,15]. Three studies have assessed the efficacy of bendamustine plus rituximab for the treatment of marginal zone lymphoma. In the first-line setting, bendamustine plus rituximab was associated with high complete response rates at the end of treatment (ranging from 71% to 98%) in patients with mucosa-associated lymphoid tissue lymphoma (n = 57)[16], intermediate-to-high-risk splenic (n = 70)[17] and nodal marginal zone lymphoma (n = 14)[18].

**Safety**

In July 2017, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update article highlighting new safety information regarding a risk of increased mortality associated with the use of bendamustine when used in non-approved combination treatment or outside approved indications[19]. Fatal toxicities were mainly due to opportunistic infections[19]. An accompanying letter sent to healthcare professionals providing the background to this safety concern refers to results from the BRIGHT and GALLIUM studies and also included unpublished post marketing safety data[20]. In the BRIGHT study mortality rates were 12 (5%) in the bendamustine plus rituximab arm and 9 (4%) in the R-CHOP group. The GALLIUM study compared safety of obinutuzumab versus rituximab in combination with CHOP, CVP or bendamustine in patients with previously untreated follicular lymphoma[21]. At a mean follow up of 34.5 months fatal adverse events were reported in 4% of patients on obinutuzumab and 3.4% of patients on rituximab. When analysed by chemotherapy used in induction, bendamustine was associated with the highest mortality rates: 5.6% (n = 19) for obinutuzumab-bendamustine and 4.4% (n = 15) for rituximab-bendamustine. Fatalities occurred in nine patients across all other arms[21]. The post marketing data showed a signal of increased frequency of opportunistic infections after treatment with bendamustine[20]. Such infections may be linked to lymphocytopenia and low CD4-positive T-cell counts which have been reported in patients for at least 7-9 months after the end of treatment[20]. The summary of product characteristics has been updated to reflect these findings[22].

A repeat literature search identified three papers with long term safety results[23-25]. Median follow up ranged from 31.2 months to 8.9 years and the indication, place in therapy and dose varied within and between studies. Across the three reports a total of 930 patients received bendamustine plus rituximab. No new safety signals arose from these studies, infection rates and secondary malignancies were in line with those previously reported[23-26].

**Cost effectiveness**

A repeat literature search identified two studies published as conference abstracts, one conducted in North America and the other in Canada[27,28]. Both compared bendamustine plus rituximab treatment with R-CHOP for the treatment of follicular lymphoma and indolent B-cell lymphomas. The first study showed that bendamustine plus rituximab was cost-effective for the first line treatment of indolent B-cell lymphomas compared with R-CHOP[28]. The analysis was performed from the health care provider perspective, with a lifetime horizon (equivalent to 24 years) and cycle lengths of six months[28]. The second study showed that over the first six months of treatment, the healthcare costs and utilisation of patients with follicular lymphoma receiving bendamustine plus rituximab was significantly lower than patients who received R-CHOP[27]. Although these studies were conducted outside of the NHS Wales healthcare setting the conclusions are in line with those reported by Dewilde et al. and summarised in the evidence status report[29,30].

**Budget impact**

Based on the small number of patients who received bendamustine plus rituximab for the treatment of marginal zone lymphoma since April 2017, it is likely that the actual budget impact is significantly lower than that estimated in the original evidence status report.

Rituximab biosimilars are now available[31,32]; however they will not directly affect the original budget impact as this was based on generic bendamustine costs alone as patients with indolent lymphoma would receive rituximab as part of any alternative regimen.

**Impact on health and social care services**

The impact on the service remains minimal.

**Patient outcome data**
[Confidential data removed.]

**References**


1. NHS England. National Cancer Drugs Fund list - version 1.68. March 2018. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed March 2018.
2. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma overview. 2018. Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma#path=view%3A/pathways/non-hodgkins-lymphoma/non-hodgkins-lymphoma-overview.xml&content=view-index. Accessed March 2018.
3. National Institute for Health and Care Excellence. Technology Appraisal 513. Obinutuzumab for untreated advanced follicular lymphoma. March 2018. Available at: https://www.nice.org.uk/guidance/TA513. Accessed March 2018.
4. National Institute for Health and Care Excellence. Technology Appraisal 491. Ibrutinib for treating Waldenstrom's macroglobulinaemia. Nov 2017. Available at: https://www.nice.org.uk/guidance/ta491. Accessed March 2018.
5. National Institute for Health and Care Excellence. Technology Appraisal 472. Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab. Aug 2017. Available at: https://www.nice.org.uk/guidance/ta472/chapter/1-Recommendations. Accessed March 2018.
6. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0717. Idelalisib (Zydelig®) 100 mg and 150 mg film-coated tablets. March 2017. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2597. Accessed March 2018.
7. Rummel MJ, Maschmeyer G, Ganser A et al. 10-year updated results from the StiL NHL1 study bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas. Presented at Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie 29 September - 3 October 2017. *Oncology Research and Treatment.* 40 (Suppl 3). https://doi.org/10.1159/000479566. Accessed March 2018.
8. Flinn I, van der Jagt R, Chang J et al. First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: results of the BRIGHT 5-year follow-up study. Presented at 14th International Conference on Malignant Lymphoma Palazzo dei Congressi, Lugano (Switzerland). 14-17 June 2017. *Journal of Clinical Oncology*. 35 (Suppl 15). http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.7500. Accessed March 2018.
9. Rummel M, Niederle N, Maschmeyer G et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomise, phase 3 non-inferiority trial. *The Lancet.* 2013;381(6):1203-1210. Available at: http://www.sciencedirect.com/science/article/pii/S0140673612617632. Accessed Jan 2017.
10. Flinn I, van der Jagt R, Kahl B et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood.* 2014;123(19):2944-2952. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260975/. Accessed Jan 2017.
11. Mondello P, Steiner N, Willenbacher W et al. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with indolent non-Hodgkin's lymphoma: evidence from a multicenter, retrospective study. *Annals of Hematology.* 2016;95(7):1107-1114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27103007. Accessed Jan 2017.
12. Mondello P, Steiner N, Willenbacher W et al. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with follicular lymphoma grade 3A: evidence from a multicenter, retrospective study. *The Oncologist.* 2018;22:1-7.
13. Laribi K, Poulain S, Willems L et al. The bendamustine plus tiruximab regimen is active and safe in previously untreated patients with Waldenstrom Macroglobulinemia, a study on behalf of the French Innovative Leukemia Organization (FILO). Presented at American Society of Hematology annual meeting. 9-12 Dec 2017. *Blood*. 130 (Suppl 4046). http://www.bloodjournal.org/content/130/Suppl_1/4046?sso-checked=true. Accessed March 2018.
14. Castillo J, Gustine J, Meid K et al. Bendamustine and bortezomib-containing regimens produce higher response rates and more durable responses versus cyclophosphamide-based therapy in frontline Waldenstrom macroglobulinemia. Presented at American Society of Hematology annual meeting. 9-12 Dec 2017. *Blood*. 130 (Suppl 1). http://www.bloodjournal.org/content/130/Suppl_1/1488. Accessed March 2018.
15. Paludo J, Abeykoon J, Hesse A et al. Bendamustine and rituximab versus dexamethasone, rituximab and cyclophosphamide in patients with Waldenstrom macroglobulinemia (WM). Presented at American Society of Hematology annual meeting. 3-6 Dec 2016. *Blood*. 128 (22):2968. http://www.bloodjournal.org/content/128/22/2968. Accessed March 2018. .
16. Salar A, Domingo-Domenech E, Panizo C et al. Long-term results of the multicenter phase II trial with bendamustine and rituximab as first line treatment for patients with MALT lymphoma (MALT-2008-01). Presented at 14th International Conference on Malignant Lymphoma Palazzo dei Congressi. 14-

17 June 2017. *Hematological Oncology*. 35 (Suppl S2). https://onlinelibrary.wiley.com/doi/epdf/10.1002/hon.2437_137. Accessed March 2018.
17. Castelli R, Bergamaschini L, and Deliliers GL. First-line treatment with bendamustine and rituximab, in patients with intermediate-/high-risk splenic marginal zone lymphoma. *Medical Oncology.* 2018;35(15).
18. Laribi K, Tempescul A, Ghnaya H et al. The bendamustine plus rituximab regimen is active against primary nodal marginal zone B-cell lymphoma. *Hematological Oncology.* 2017;35(4):536-541.
19. Medicines and Healthcare products Regulatory Agency. Drug safety update. Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatits B reactivation. July 2017. Available at: https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-mortality-observed-in-recent-clinical-studies-in-off-label-use-monitor-for-opportunistic-infections-hepatitis-b-reactivation. Accessed March 2018.
20. Astellas Direct Healthcare Professional Communication. Bendamustine (Levact): increased mortality observed when used in non-approved combination treatments or outside the approved indications. July 2017. Available at: https://assets.publishing.service.gov.uk/media/5947f270ed915d20f8000271/Bendamustine_DHPC.pdf. Accessed March 2018.
21. Castellino AM. Obinutuzumab bests rituximab in advanced FL. *Medscape.* 2016. Available at: https://www.medscape.com/viewarticle/872744.
22. Napp Pharmaceuticals Limited. Levact®. Summary of Product Characteristics. March 2018. Available at: https://www.medicines.org.uk/emc/product/5656. Accessed March 2018.
23. Penne M, Yazdy MS, Nair KS et al. Extended follow-up of patients treated with bendamustine for lymphoid malignancies. *Clinical Lymphoma, Myeloma & Leukemia.* 2017;17(10):637-644.
24. Martin P, Chen Z, Cheson BD et al. Long-term outcomes, secondary malignancies and stem cell collection following bendamustine in patients with previously treated non-Hodgkin lymphoma. *British Journal of Haematology.* 2017;178(2):250-256.
25. Olszewski A, Reagan J, and Castillo JJ. Late infections and secondary malignancies after bendamustine/rituximab or RCHOP/RCVP chemotherapy for B-cell lymphomas [correspondence]. *American Journal of Hematology.* 2018;93(1):E1-E3.
26. All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Bendamustine plus rituximab (MabThera®) for treating mantle cell lymphoma. March 2017. Available at: https://www.awttc.org/pams/current-one-wales-interim-commissioning-decisions. Accessed March 2018.
27. Zhou J, Pathak A, Brander D et al. Differences in health care costs and utilization: BR vs RCHOP in patients with follicular lymphoma. Presented at American Society of Clinical Oncology (ASCO) 2017 annual meeting. 2-6 June 2017. *Journal of Clinical Oncology.* 35 (Suppl 15). http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e19049. Accessed March 2018.
28. Aw A, Coyle K, Bence-Bruckler I et al. Bendamustine and rituximab versus conventional chemoimmunotherapy as a frontline treatment for patients with indolent B-cell lymphoma: a cost-effectiveness analysis. Presented at American Society of Hematology 58th annual meeting and exposition. 3-6 Dec 2016. *Blood.* 128 (22). http://www.bloodjournal.org/content/128/22/1186?sso-checked=true. Accessed March 2018.
29. Dewilde S, Woods B, Castaigne JG et al. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. *Journal of Medical Economics.* 2014;17(2):111-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24308372. Accessed Feb 2017.
30. All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed indolent lymphomas. March 2017. Available at: https://www.awttc.org/pams/current-one-wales-interim-commissioning-decisions. Accessed March 2018.
31. Sandoz Limited. Rixathon®. Summary of Product Characteristics. Dec 2017. Available at: https://www.medicines.org.uk/emc/product/2714. Accessed March 2018.
32. Napp Pharmaceuticals Limited. Truxima®. Summary of Product Characteristics. Feb 2018. Available at: https://www.medicines.org.uk/emc/product/8878. Accessed March 2018.