# Bendamustine–Rituximab (BR) [NHL]

## INDICATIONS

Unlicensed* / NHS funded: **NON-HODGKIN LYMPHOMA (NHL)** [ICD-10 codes: C82, C83, C85]

- Treatment naïve low grade non-Hodgkin lymphoma [**Blueteq** required]
- Treatment naïve mantle cell non-Hodgkin lymphoma (MCL) [**Blueteq** required]
- Relapsed low grade non-Hodgkin lymphoma [**Blueteq** required]

*Unlicensed indication: Bendamustine in combination with Rituximab for NHL. Ensure compliance with local Trust governance framework.

**Note: Two BR protocols exist – one for NHL and one for CLL. This protocol is for NHL. Please ensure it is the correct one for the patient's diagnosis.**

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## TREATMENT INTENT

Disease modification

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## PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage and IPI of disease - CT scan (neck, chest, abdomen and pelvis), and/or PET-CT scan, presence or absence of B symptoms, clinical extent of disease. Consider bone marrow aspirate and trephine.
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, $\beta_2$ microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) when indicated [H.8], group and save.
4. Send a "**group and save"** sample to transfusion and ensure patient has been flagged to blood bank for the requirement of **irradiated blood products** for all future transfusions. Refer to [Guidelines for the use of blood components in adult haematology]. Ensure irradiation card is given to the patient.
5. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
6. ECG +/- ECHO – if clinically indicated.
7. Record performance status [ECOG].
8. Record vital signs, height and weight.
9. Consent and counseling – ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
10. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Assess and document tumour lysis risk as part of pre-assessment. Patients should be adequately hydrated before and after each cycle administration. In bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Refer to the Tumour Lysis Syndrome in Adults protocol [H.8]. **When Allopurinol is indicated – advise patients NOT to take it on days of Bendamustine** due to the risk of skin reactions (see DRUG INTERACTIONS below).
12. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Treatment should be agreed in the relevant MDT.

## DRUG REGIMEN

| Day(s) | Drug | Dose | Route | Administration details |
|---|---|---|---|---|
| 1 | Paracetamol<br>Hydrocortisone<br>Chlorphenamine | 1000 mg<br>100 mg<br>10 mg | PO<br>IV<br>IV | ≥ 30 minutes before Rituximab |
| **1** | **RITUXIMAB** | **375 mg/m²** | **IV** | In 500 mL sodium chloride 0.9%<br>[Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400 mg/hour]. Patients should be observed for 30 minutes before the start of other infusions. If first dose is well tolerated, consider a rapid infusion rate from cycle 2 onwards. |
| **1–2** | **BENDAMUSTINE** | **90 mg/m²** | **IV** | in 500 mL sodium chloride 0.9%<br>over 30-60 minutes |
| CYCLE FREQUENCY: 28 days | | | | |
| TREATMENT DURATION: max. 6 cycles | | | | |

## CONCURRENT MEDICATIONS

| | |
|---|---|
| **TLS prophylaxis**<br>[Cycle 1] | Refer to the Tumour Lysis Syndrome in Adults protocol [H.8].<br>**Note: Allopurinol should be omitted on the days of Bendamustine.**<br>(see DRUG INTERACTIONS below).<br><br>**TLS risk** / **TLS prophylaxis – Cycle 1**<br>Low: Hydration + Allopurinol 300mg OD*, starting **from day 3** for 7 days<br>Intermediate: Hydration + Allopurinol 300mg OD*, starting **3 days before Bendamustine,** then **omit on Bendamustine days,** and **restart from day 3** for 7 days (10 days in total)<br>High risk: Hydration + Rasburicase 3mg on days of Bendamustine, unless otherwise indicated by the Clinician.<br><br>*Reduce dose in renal impairment. |
| **Antiviral prophylaxis** | Aciclovir 200mg TDS during treatment and for 3 months after completion |
| **PJP prophylaxis** | Co-trimoxazole 480mg three times a week on Mon/Wed/Fri for duration of treatment and at least 3 months after completion. Consider reducing the dose to 480 mg twice weekly during neutropenic periods. Pentamidine can be considered for patients who are intolerant or allergic to Co-trimoxazole. |
| **Anti-emetics**<br>Days 1–2:<br>Moderate risk | ▪ Ondansetron on days 1-2: 8mg BD<br>▪ Metoclopramide on days 1-5: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required.<br>For alternative options, refer to [TVCA Anti-emetic guideline]. |

## CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Severe liver impairment (Bendamustine). Refer for full details to the relevant Summary of Product Characteristics (SmPCs).

## INVESTIGATIONS

Before each cycle: FBC, renal and liver profiles. ECG when clinically indicated (monitor closely in patients with cardiac disorders).

## RESTAGING

Consider a response assessment with CT NCAP after 3–4 cycles with the end of treatment CT NCAP or PET/CT.

- For marginal zone lymphoma, consider stopping at 4 cycles if good response.
- For other indications, usually continue to 6 cycles.

## TREATMENT MODIFICATIONS

**All modifications should be discussed with the Consultant.**

| **Haematological toxicities** |
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| If neutrophil count < 1 x $10^9$/L or platelets < 75 x $10^9$/L, consider delaying treatment by 1 week. |

| **Non-haematological toxicities** | |
|---|---|
| **Grade 3 or 4 toxicities** | Discuss with Consultant – next cycle should be delayed until toxicity grade is ≤ 2. |

| **Tumour lysis syndrome** (TLS) Grade 3 or 4 |
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| Following complete resolution of TLS, treatment may be restarted at the full/current doses during the next scheduled cycle in conjunction with prophylactic therapy. |

| | **Renal impairment** | **Hepatic impairment** |
|---|---|---|
| **Bendamustine** | GFR > 10 mL/min: 100% dose<br>GFR ≤ 10 mL/min: limited data, clinical decision | Mild (bilirubin < 20 µmol/L): 100% dose<br>Moderate (bilirubin 20–51 µmol/L): 70% dose<br>Severe (bilirubin > 51 µmol/L): not recommended |

## DRUG INTERACTIONS

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| **Bendamustine** | ▪ Concomitant use with CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, aciclovir, cimetidine) may increase Bendamustine concentration. Use with caution.<br>▪ Cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported when Bendamustine and Allopurinol were administered concomitantly – avoid concurrent use. |
| **Rituximab** | Since hypotension may occur during Rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to infusion. |

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

### Rituximab

- Infusion related reactions (IRRs) or severe cytokine release syndrome, characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. **Hepatitis B reactivation** – see the pathway for the management of an HBV-positive patient [LPW.21].

**Bendamustine**

- Haematological adverse reactions, including leukopenia, thrombocytopenia (dose titration may be required)
- Constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting)
- **Infections**: including bacterial (sepsis, pneumonia) and opportunistic infections (Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV)). Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following use of Bendamustine mainly in combination with Rituximab or Obinutuzumab. **Hepatitis B reactivation** – see the pathway for the management of an HBV-positive patient [LPW.21]. Increased mortality (mainly due to opportunistic infections) was observed in recent clinical studies when Bendamustine was used in combination treatment outside the approved indications.
- **Dermatologic toxicities** – allergic reactions, urticaria (common). Cases of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) have been reported in patients who received Bendamustine and Allopurinol simultaneously (avoid concurrent use). Patients who experience any skin reactions during treatment, should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with Bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly. Cases of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) have been reported.
- Refer to the **MHRA advice** for healthcare professionals:
  - [MHRA Drug Safety Update. 2017]. Advise patients to **report promptly any new signs of infection**, including fever or respiratory symptoms, and consider discontinuing Bendamustine if there are signs of opportunistic infections. Monitor patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events. Monitor known carriers of **HBV** for signs and symptoms of active HBV infection. Report suspected adverse reactions associated with Bendamustine to MHRA via [Yellow Card], including those associated with off-label use.
  - [MHRA Drug Safety Update. 2021]. Periodically perform **skin examinations** in patients on Bendamustine-containing regimens and **consider PML** in the differential diagnosis for patients on Bendamustine with new or worsening neurological, cognitive, or behavioural signs or symptoms.

## EXTRAVASATION RISK

Bendamustine: vesicant / irritant
Rituximab: neutral

## TREATMENT RELATED MORTALITY

< 1%

## REFERENCES

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3. Rummel MJ et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol. 2005 May 20;23(15):3383-9.
4. Robinson KS et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008 Sep 20;26(27):4473-9.
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6. Seacross Pharmaceuticals Ltd. Bendamustine Hydrochloride 2.5mg/ml powder for concentrate for solution for infusion. Last updated 21/05/2025. Available at http://www.medicines.org.uk/emc. <Last accessed 25/09/2025>
7. MHRA. Drug Safety Update. Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation. Published 20/07/2017. 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 <Last accessed 25/09/2024>
8. MHRA. Drug Safety Update. Bendamustine (Levact): increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML). Published 24/03/2021. Available at https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-risk-of-non-melanoma-skin-cancer-and-progressive-multifocal-encephalopathy-pml#contents <Last accessed 25/09/2024>
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## CORRESPONDING DOCUMENTS

Bendamustine-R (NHL) Nursing Care Plan [N-L.45]

## REVIEW

| Name | Revision | Date | Version | Review date |
|---|---|---|---|---|
| Cheuk-kie Jackie Cheung, Haematology Pharmacist | Document name changed. Co-trimoxazole added and generic changes to support medication section. | Sep 2018 | 2.1 | |
| NSSG Lymphoma Group | Annual protocol review | May 2019 | 2.2 | May 2021 |
| Quality Manager | Nursing care plan added | Oct 2020 | 2.3 | May 2021 |
| Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma & CLL Group | Restaging, Contraindications, Drug interactions added. Drug regimen/Concurrent medications, Adverse effects, References updated. MHRA advice on Bendamustine use added. Nursing Care Plan as corresponding document. General formatting. Annual protocol review. | September 2024 | 3.0 | September 2027 |