reference no: 2404
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Clinical Commissioning Policy:

# Combination brentuximab vedotin and bendamustine for patients aged 8 years and above with relapsed or refractory classical Hodgkin lymphoma [2404]

## Summary

Brentuximab vedotin and bendamustine is recommended to be available as a routine commissioning treatment option for patients aged 8 years and above in relapsed and refractory classical Hodgkin lymphoma within the criteria set out in this document.

## Committee discussion

Clinical Panel recommends that this policy progresses as a routine commissioning policy. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here: Clinical Commissioning Policy: Combination brentuximab vedotin and bendamustine for patients aged 8 years and above with relapsed or refractory classical Hodgkin lymphoma

## What we have decided

NHS England has carefully reviewed the evidence to treat relapsed or refractory classical Hodgkin lymphoma (for patients aged 8 years and above) with brentuximab vedotin and bendamustine. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: Clinical Commissioning Policy: Combination brentuximab vedotin and bendamustine for patients aged 8 years and above with relapsed or refractory classical Hodgkin lymphoma

This should not be relied upon as a statement of the effectiveness of any technology appraisal guidance published by NICE. Clinicians should ensure they keep up to date with evidence about available treatments.

## Links and updates to other policies

NHS England has previously published a not for routine commissioning position for single agent bendamustine for relapsed or refractory classical Hodgkin lymphoma (all ages):

- Clinical Commissioning Policy Statement 200701P: Bendamustine for relapsed/refractory classical Hodgkin lymphoma (all ages) (NHS England 2020)

NHS England has no other published clinical policies directly relating to the use of dual therapy with brentuximab vedotin and bendamustine for the above indication. However, this policy is linked to:

- Clinical commissioning policy 170055P: Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's lymphoma (all ages) (NHS England 2018)
- Clinical Commissioning Policy 170054P: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages) (NHS England 2018)
- Clinical Commissioning Policy 17088P: Bendamustine with rituximab for first line treatment of mantle cell lymphoma (all ages) (NHS England 2018)
- Clinical Commissioning Policy Statement 200701P: Bendamustine for relapsed/refractory classical Hodgkin lymphoma (all ages) (NHS England 2020)
- Technology appraisal guidance 524: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (NICE 2018)
- Technology appraisal guidance 772: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies (NICE 2022)
- In development [GID-TA11384]: Brentuximab vedotin in combination for untreated stage 3 or 4 CD30-positive Hodgkin lymphoma [ID6334] (NICE, expected publication date: 07 May 2025)

# Plain language summary

## About relapsed/refractory classical Hodgkin Lymphoma

Classical Hodgkin lymphoma (cHL) is an uncommon blood cancer in which white blood cells start to grow in an uncontrolled way and form tumours in the lymph nodes and/or other parts of the body. Frontline therapy is highly effective and cures the majority of patients, but approximately 10-30% of patients will develop relapsed or refractory (R/R; resistant) disease. Clinicians will use the word 'relapse' if cancer returns following a period of remission. 'Refractory' means does not respond well enough to initial treatment.

## About current standard treatments

The first phase of treatment for R/R cHL is known as induction therapy. The aim is to eliminate as many cancer cells as possible to achieve remission (disappearance of lymphoma on scans). This usually consists of multi-drug chemotherapy initially (second-line treatment).

Once a patient achieves remission, they proceed to the second step known as consolidation treatment. The goal of consolidation therapy is to prevent cancer from returning. Consolidation treatment usually consists of stem cell transplant (SCT) and is potentially curative. This involves giving very high-dose chemotherapy to treat the lymphoma, then replenishing a patient's blood stem cells to help them recover. Without

SCT, treatment is considered palliative, and most patients will ultimately develop progressive disease.

However, to receive SCT, patients need to have an adequate response to induction chemotherapy. Only half of patients respond well enough to second-line chemotherapy. Of those who respond well, at least a quarter will relapse again and need further treatment. Therefore, most patients with R/R cHL require additional induction therapy (third-line treatment).

In the last decade, NICE have approved two targeted drugs as third-line or later treatment for R/R cHL: brentuximab vedotin (BV; TA524) and pembrolizumab (TA772), a type of immune therapy (PD-1 inhibitor). However, only a minority (25-34%) of patients have sufficient response to proceed directly with subsequent SCT (Eyre et al, 2017).

### About bendamustine and brentuximab vedotin

BV is an antibody-drug conjugate which is licenced and NICE approved for use in cHL (TA524). It works by binding to a protein on the cancer cell surface (CD30) and delivers a cytotoxic molecule to the cancer cells. This stops them from dividing and the cancer cell eventually dies.

Bendamustine is an alkylating chemotherapy drug. It works by inducing DNA damage and cross-linking DNA strands, which inhibits the ability of cancer cells to grow and survive. It has demonstrated clinical efficacy in several lymphoid malignancies, including non-Hodgkin lymphoma and cHL. However, its use in the treatment of R/R cHL, as well as in combination with BV, are off-label.

Recent studies have found high response rates and SCT rates with the combination of BV with bendamustine (BVB), much higher than reported with current third-line treatments, i.e. brentuximab or pembrolizumab alone. Treatment with BVB is also shorter than BV or pembrolizumab monotherapy and reduces the need for subsequent therapies.

## Epidemiology and needs assessment

The incidence of Hodgkin lymphoma in the UK is 3.3/100,000 persons/year, equating to 2124 new diagnoses per year in 2016-2018, which is predicted to rise to 2900 cases/year by 2040. The median age at diagnosis is around 40 years but it affects a broad age range: it is the most common cancer in the teen and young adult age group (15-24 years) and 13% of cases diagnosed in the over-75s. There is a slight male preponderance.

Data on numbers of patients treated for R/R cHL are not publicly available. Approximate numbers can be extrapolated from British Society for Bone and Marrow Transplantation data, which report that approximately 150 patients receive ASCT for R/R cHL and 40-50 patients receive allogeneic SCT per annum across the UK (2016-2020). It is assumed that majority of these patients (>80%) will be treated in England and 60-70% will have required three lines of induction therapy, either for suboptimal response to second line therapy or subsequent relapse. Noting that some patients will not proceed with SCT due to inadequate response, it is estimated that 150-200 patients in England per annum will be eligible for this policy.

## Implementation

NHS England will routinely commission dual therapy with BVB in accordance with the patient pathway for individuals meeting all of the following inclusion criteria, and none of the exclusion criteria.

## Inclusion criteria

Patients aged 8[1] years and older with biopsy proven, CD30-positive refractory or relapsed cHL should be considered for treatment with BVB if they meet the following criteria:

- An Eastern Cooperative Oncology Group (ECOG) Score of ≤2 at baseline for adults

**OR**

- A Karnofsky (for patients aged >16 years) **OR** Lansky (for patients aged ≤16 years) performance status ≥60 for children

**AND**

- Failure of at least 2 prior lines of therapy for cHL

**OR**

- Have already had autologous stem cell transplant

**AND**

- Has been assessed by a lymphoma multi-disciplinary team (MDT) or paediatric MDT[2], liaising with regional transplant centres where necessary.

## Exclusion criteria

Patients are excluded if they meet **ANY** of the following exclusion criteria:

- Previously treated with bendamustine
- Less than a partial or a complete response to previous treatment with brentuximab vedotin
- Contraindications to either brentuximab vedotin or bendamustine
- Pre-existing neuropathy grade 3 or greater

## Starting criteria

The initiation of BVB should be managed by a physician(s) with experience in the treatment of cHL with the continued support of the lymphoma MDT. Children, teenage and young adult (TYA) patients should be managed by a children's or TYA principal treatment centre MDT, in accordance with service specifications.

## Stopping criteria

Treatment will be stopped in patients who meet ANY of the following criteria:

[1] This age limit for this policy has been restricted in line with the independent evidence review.
[2] The paediatric MDT include at least two consultants in the subspecialty with active and credible expertise in the relevant field of whom at least one must be a consultant paediatrician. The MDT should include a paediatric pharmacist and other professional groups appropriate to the disease area.

- Patients with relapsed or refractory cHL who are determined by the treatment clinician to have been optimised for SCT
- A maximum treatment duration of 6 cycles of combination therapy
- By 3 cycles, if response assessment demonstrates a response status of less than a partial or a complete response
- Unacceptable toxicity
- Patient or carer decision to stop treatment

## Dosing

BV has a GB Product Licence which includes the following indications of relevance:

- Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
    - following ASCT, or
    - following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

The use of bendamustine, in combination with BV, for the treatment of R/R cHL is off-label.

Paediatric patients (between 8 and 18 years)

The recommended dosage of BV for paediatric patients is 1.8mg/kg (maximum of 180mg total dose) administered by intravenous infusion over 30 minutes on day 1 of the treatment cycle.

The recommended dosage of bendamustine for paediatric patients is 90 mg/m² administered by intravenous infusion over 60 minutes on days 1 and 2 of a 21-day cycle.

Adult patients (18 years and over)

The recommended dosage of BV for adults is up to 1.8 mg/kg (maximum of 180mg total dose) administered by intravenous infusion over 30 minutes on day 1 of the treatment cycle.

The recommended dosage of bendamustine for adults is up to 90 mg/m² administered by intravenous infusion over 60 minutes on days 1 and 2 of a 21-day cycle.

Dose reduction and/or dose interruption may be required based on individual safety and/or tolerability. This should be determined by the treating clinician.

Pre-medication should also be considered particularly in the case of infusion reactions. Clinicians are recommended to consult the Summary of Product Characteristics (SmPC) on brentuximab vedotin (SmPC) and bendamustine (SmPC).

Treatment breaks of up to 6 weeks for paediatric and adult patients are permitted.

## Patient pathway

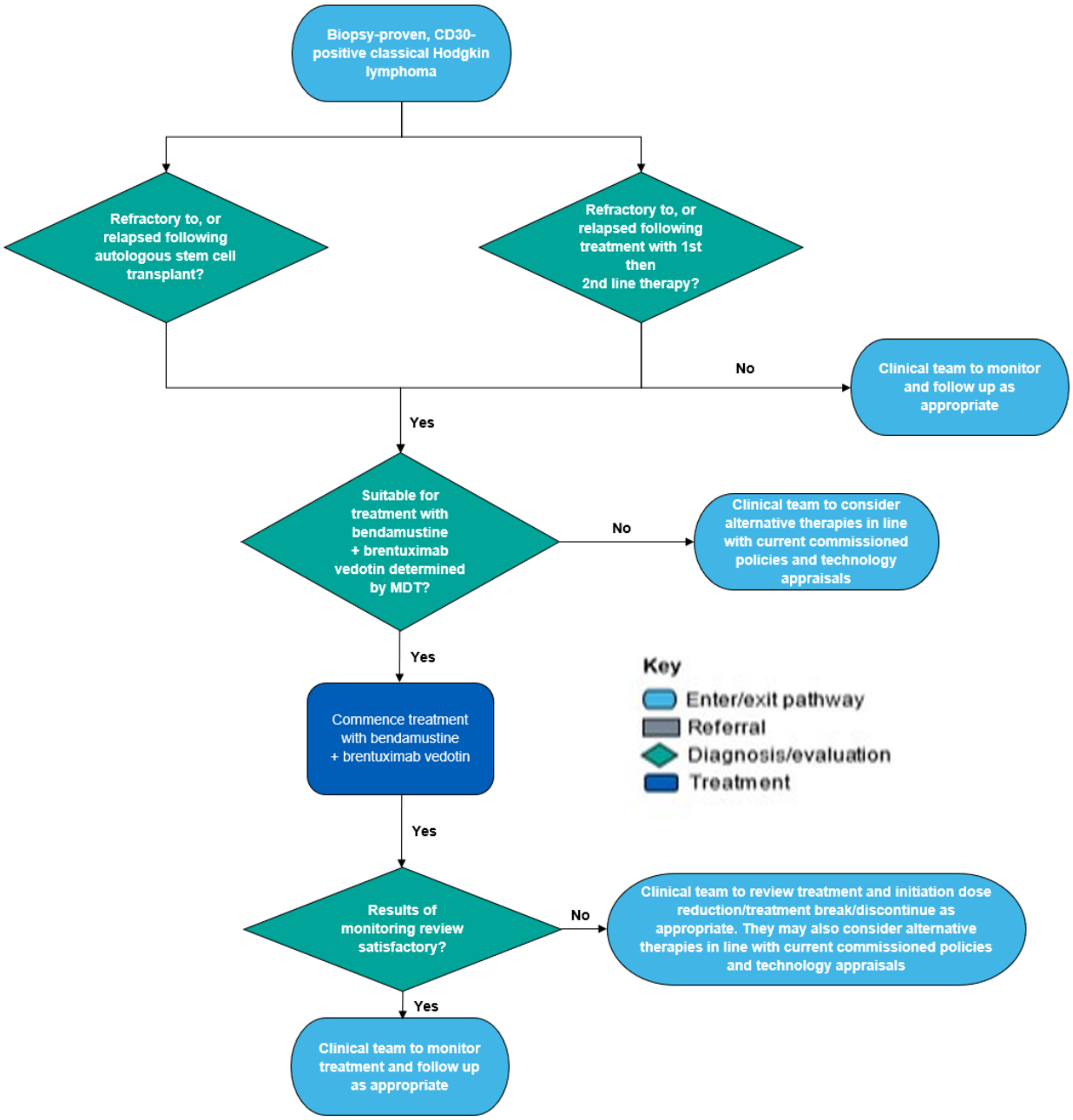


Figure 1 – patient pathway for classical Hodgkin Lymphoma

# Governance arrangements

Service Specifications:

- CANCER: CHEMOTHERAPY (ADULT)
- Children's Cancer Network - Principal Treatment Centres
- Specialist cancer services for children and young people: Teenage and Young Adults Principal Treatment Centre Services

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process. BVB must only be used for treatment in specialised centres or in collaboration with specialised centres under the supervision of a multi-disciplinary team.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

## Mechanism for funding

BVB are categorised as high-cost drugs. BV is to be reimbursed under the cost and volume process and bendamustine is reimbursed within the trust's fixed 'block' arrangement.

## Audit requirements

All systemic anti-cancer treatments (SACT) must be recorded via the SACT portal as required within the NHS standard contract. There are no specific audit requirements, however data collection using case report forms (CRF) to facilitate a multicentre service evaluation is strongly encouraged.

## Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

## Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Definitions

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| Antineoplastic | Agents or treatments that inhibit or prevent the growth and spread of tumours or malignant cells. |
| Alkylating | Compounds that work by adding an alkyl group to the guanine base of the DNA molecule, preventing the strands of the double helix from linking as they should. |
| Autologous stem cell transplant | Stem cells derived or transferred from the same individual's body |
| Chemotherapy | A cancer treatment where medicine is used to kill cancer cells. The most common types of chemotherapy are either given into a vein (intravenous) or as chemotherapy tablets (oral chemotherapy) |
| Conjugate | A compound created by chemically joining two or more different substances |
| Lymphatic system | A network of vessels that drain lymph from tissues and play a key role in the immune system. |
| Refractory | A type of cancer that does not respond to treatment or becomes resistant to treatment. For the purposes of this policy, refractory disease is defined as a failure to achieve at least a partial response (PR) at the end of treatment with cladribine, or in the case of pentostatin, this would be at 6 months from the end of treatment. |
| Relapsed | When cancer returns after a period of remission. |

## References

Eyre, T.A., Phillips, E.H., Linton, K., Arvind Arumainathan, Kassam, S., Gibb, A., Allibone, S., Radford, J., Peggs, K.S., Combes, B., Stewart, G., Rifca Ledieu, Booth, C., Osborne, W., Miall, F., Eyre, D.W., Ardeshna, K.M. and Collins, G.P. (2017). Results of a multicentre UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the transplant naive setting. British Journal of Haematology, 179(3), pp.471–479. doi:https://doi.org/10.1111/bjh.14898.