Data in the R/R HL second salvage setting brentuximab vedotin▼ core data deck

This educational resource has been developed and funded by Takeda UK Ltd. and is intended for healthcare professionals only.
Prescribing information can be found on slide 13.

R/R HL, relapsed or refractory Hodgkin lymphoma.

UK/ADC/1707/0051j(1) Date of preparation: March 2018

Brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma:

1. following autologous stem cell transplant (ASCT)
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
3. at increased risk of relapse or progression following ASCT

NOVIGATE

Brentuximab vedotin (ADCETRIS) Summary of Product Characteristics.

UK real world evidence for brentuximab vedotin as second salvage therapy in transplant-naive R/R HL patients[1]

Design: Retrospective, multicentre study of 99 patients with relapsed or refractory cHL treated with brentuximab vedotin monotherapy at nine large UK centres (May 2011–July 2016)

Patients:

Eligibility:

- SCT naïve
- Previously received ≥2 prior chemotherapy lines with curative intent

All went on to receive brentuximab vedotin with the intention of subsequent SCT

Data at diagnosis and relapse were collected from hospital records by the treating physician*

Risk factors for poor PFS at first relapse** and treatment details for first, second and third lines including regimen were captured

Treatment data included;

- Best ORR by PET-CT or CT alone
- Duration of first remission
- Total number of therapy lines prior to brentuximab vedotin

For AE data, grading of AEs were collected wherever available according to CTCAE

*Age, gender, LDH, ECOG performance status, extranodal disease, B symptoms, Ann Arbor stage, disease bulk, histological subtype

**Hb, extranodal disease, B symptoms, Ann Arbor stage[2]

AE, adverse event; cHL, classical Hodgkin lymphoma; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology group; Hb, haemoglobin; LDH, lactate dehydrogenase; ORR, overall response rate; PET, positron emission tomography; PFS, progression free survival; R/R HL, relapsed or refractory Hodgkin lymphoma; SCT, stem cell transplant.

1. Eyre T, et al. *Br J Haematol*. 2017;179:471–479; 2. Moskowitz et al. *Blood* 2001;97:616–623.

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UK real world evidence for brentuximab vedotin as second salvage therapy in transplant-naive R/R HL patients

Baseline patient characteristics:

Characteristics	BV SCT-naïve patients (n = 99)
At diagnosis	
Median age (years) at diagnosis	32 years (range 13–70 years)
Gender Male / Female	 45 (45%) / 54 (55%)
ECOG at diagnosis (n = 86) 0 1 >1	 45 (52%) 36 (42%) 5 (5%)
Histological subtype at diagnosis (n =89) Nodular sclerosis	 75 (84%)
Ann Arbor staging at diagnosis (n = 98) 1-2 3-4	 28 (29%) 70 (71%)
Bulk at diagnosis > 10 cm (n = 95)	20 (21%)
Length of first remission: Earliest remission to relapse (n = 66)	Median 6.0 months (range 0. – 74.0 months)

Risk factors at relapse	
Haemoglobin (n = 80) <12	41 (51%)
Extranodal disease at first relapse (n = 94)	44 (47%)
B symptoms at first relapse (n = 88)	33 (38%)
Ann Arbor stage at first relapse (n = 94) 3-4	 67 (71%)
Median time from last treatment to BV (n = 94)	2.5 months (range 0.7–34.8 months)
Median time from initial diagnosis to BV (n = 99)	14.5 months (range 4.0–190.9 months)
Prior lines of therapy pre BV (n = 99) 2 3 4	 70 24 5
Cycles of BV given	Median 4 (range 1–9)

BV, brentuximab vedotin; ECOG, Eastern Cooperative Oncology Group; R/R HL, relapsed or refractory Hodgkin lymphoma; SCT, stem cell transplant.

1. Eyre T, et al. *Br J Haematol*. 2017;179:471–479.

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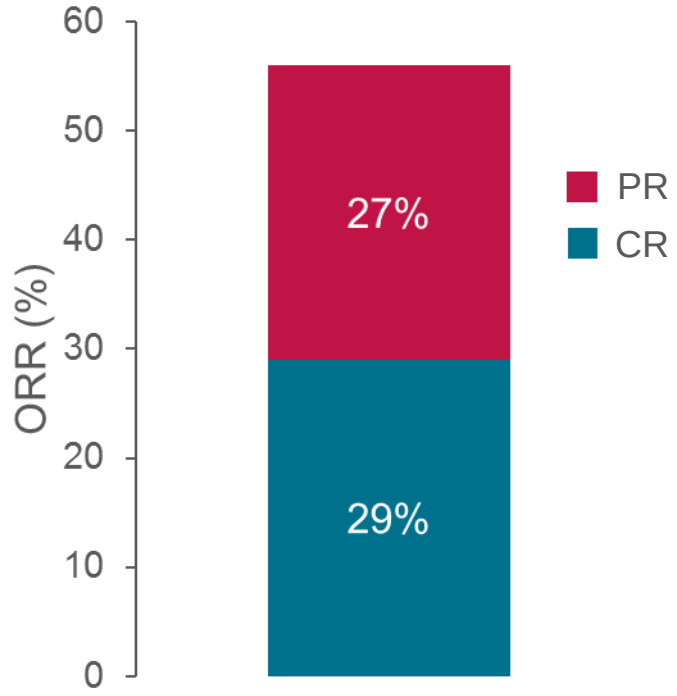
UK real world evidence for brentuximab vedotin as second salvage therapy in transplant-naive R/R HL patients



ORR for all BV patients as assessed by the local treating physician

BV demonstrated an ORR of 56% enabling a bridge to SCT in a cohort of high risk SCT-naive, predominantly refractory cHL patients

Response rates were consistent with other studies

Median follow up from the start of BV: 12.0 months (0.4–56.7 months)

ORR for all patients = 56%

Median PFS: 5.6 months (95% CI 4.4–12.2 months)

Median OS: 37.2 months (95% CI 18.3 months–NR)

Patients achieving CR produced more durable remissions (CR median DOR NR vs PR median PFS 6.5 months (95% CI 4.7–NR))

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; cHL, classic Hodgkin lymphoma; CI, confidence interval; CR, complete remission; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PR, partial remission; R/R HL, relapsed or refractory Hodgkin lymphoma; SCT, stem cell transplant.

1. Eyre T, et al. *Br J Haematol*. 2017;179:471–479.

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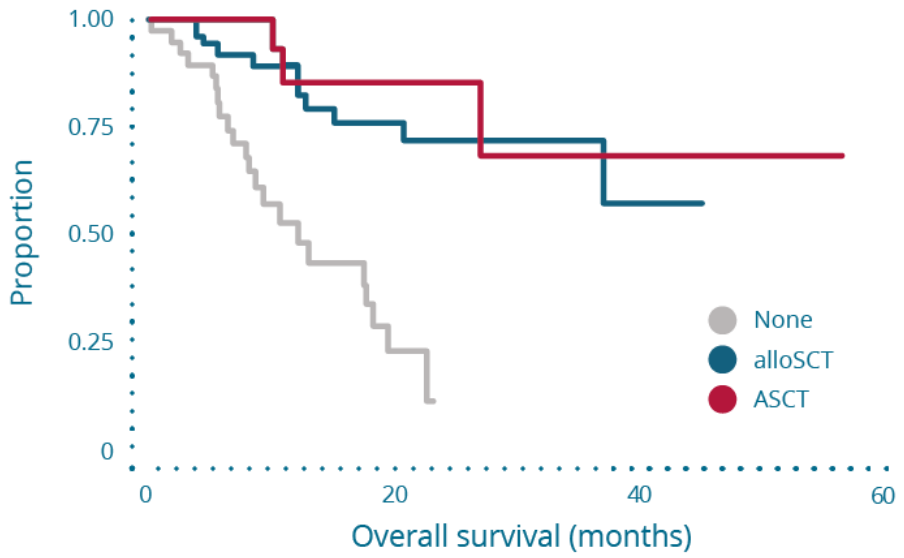
UK real world evidence for brentuximab vedotin as second salvage therapy in transplant-naive R/R HL patients

Overall survival according to subsequent intervention



No. at risk (events)				
None	38	3	0	0
alloSCT	38	18	4	0
ASCT	23	8	1	0

No SCT (median PFS 3.0 mos (95% CI 2.5–4.4) and median OS 12.2 mos (95% CI 8.1–18.3 mos)) vs ASCT (median PFS NR (95% CI 17.0 mos–NR) and median OS NR (95% CI 27.0 mos–NR)) vs alloSCT (median PFS NR (95% CI 5.6 mos–NR) and median OS NR (95% CI 37.2 mos–NR))

Survival outcomes and the BV treatment pathway:

- 34% proceeded directly to consolidation SCT after a median of four cycles of BV
- 27% underwent deferred SCT after additional treatment
- 39% did not reach SCT and have poor outcomes, with PFS of 3.0 months
- Patients consolidated with SCT (auto or allo) had a superior PFS and OS
- BV was judged to be relatively non-toxic in this real world setting in ASCT naïve R/R HL patients

AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; CI, confidence intervals; NR, not reached; OS, overall survival; PFS, progression free survival; R/R HL, relapsed or refractory Hodgkin lymphoma; SCT, stem cell transplant.

1. Eyre T, et al. *Br J Haematol*. 2017;179:471–479.

NOVIGATE

Brentuximab vedotin in patients with R/R HL who are ineligible for ASCT: A Germany and United Kingdom retrospective study

Objective: To describe real-world outcomes with BV in patients with R/R HL considered ASCT ineligible or who refuse ASCT

Design: Retrospective medical chart review study that enrolled patients at 45 clinical sites representative of routine practice in Germany and the UK

Inclusion criteria:

- >18 years at time of HL diagnosis
- Progressed after ≥2 multi-drug chemotherapy regimens between 1 January 2008 and 30 June 2014
- Not candidates for ASCT as identified by their clinicians
- Subsequently treated with BV

Outcomes: Best response to treatment, progression-free survival and overall survival

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; R/R HL, relapsed or refractory Hodgkin lymphoma.

Bröckelmann PJ, et al. *Eur J Haematol* 2017;99:553–558.

NOVIGATE

Brentuximab vedotin in patients with R/R HL who are ineligible for ASCT: A Germany and United Kingdom retrospective study

Results:

- 136 patients (78 in Germany and 58 in the UK) were included in the study*
- At relapse, prior to BV, 54% of patients had stage III or IV disease, 9.6% had bulky disease, and 61.0% had an ECOG status ≥2
- Most common reasons for ASCT ineligibility:** Comorbidities, 73.5%; age, 56.6%
- Patients received a median of 8 cycles of BV (range 6–15)
- Median duration of follow-up: 10.9 months (range, 0.4–47.0 months)

Efficacy:

- Overall response rate 74%
- Complete response 34.6%

BV treatment response, any post-relapse line of treatment

	Germany N=78	UK N=58	All countries N=136
No. of cycles, median (IQR)	9.0 (8.0–12.0)	8.0 (4.0–10.0)	8.0 (6.0–11.5)
Best response			
CR	28 (35.9)	19 (32.8)	47 (34.6)
PR	36 (46.2)	18 (31.0)	54 (39.7)
SD	3 (3.8)	15 (25.9)	18 (13.2)
PD	11 (14.1)	6 (10.3)	17 (12.5)

*14/78 (17.9%) patients in Germany and 6/58 (24.1%) in the UK had documented use of BV as the first line of therapy after relapse. Of note, the study investigators confirmed that all patients met study eligibility criteria, and thus, it is possible that radiotherapy was counted as a line of therapy.

** Multiple reasons for ASCT ineligibility could be selected.

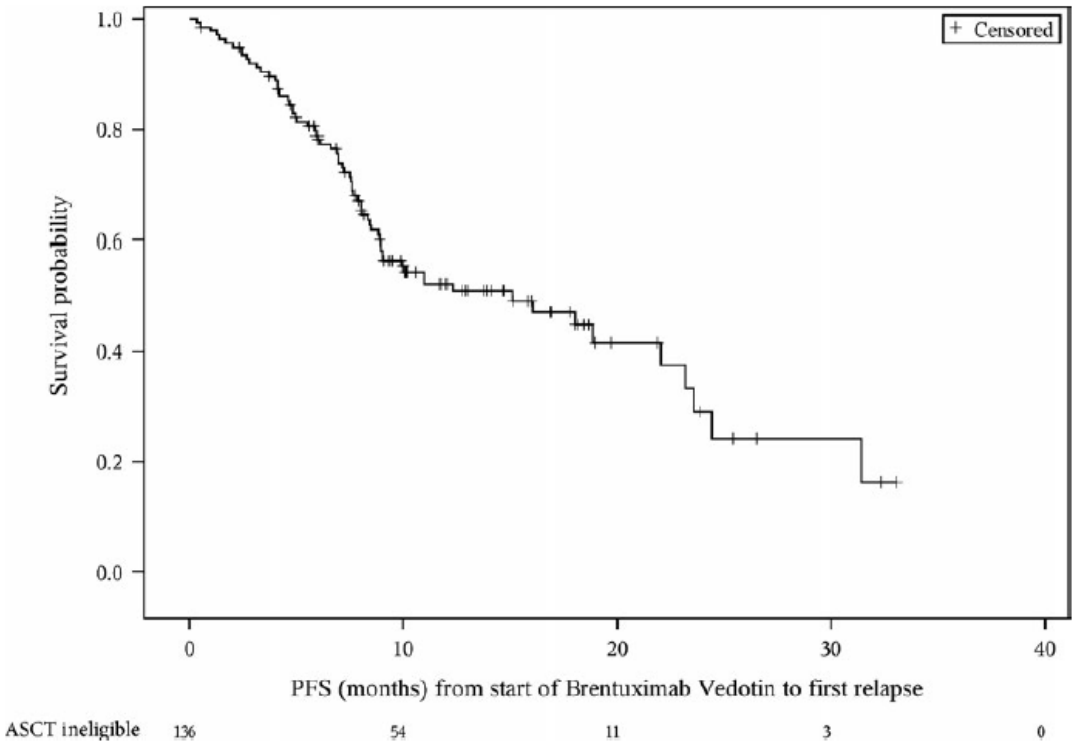
ASCT, autologous stem cell transplant; BV, brentuximab vedotin; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD, progressive disease; PR, partial response; R/R HL, relapsed or refractory Hodgkin lymphoma; SD, stable disease.

Bröckelmann PJ, et al. *Eur J Haematol* 2017;99:553–558; Bröckelmann PJ, et al. Poster presentation 305. Presented at EHA 2017.

NOVIGATE

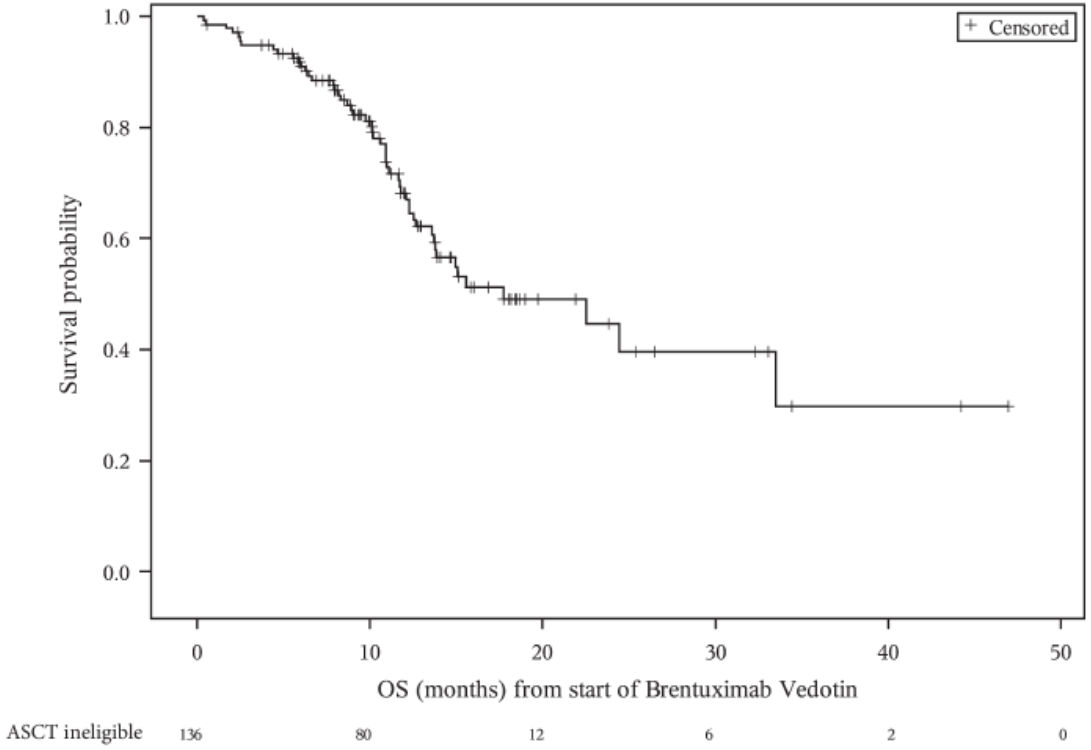
Brentuximab vedotin in patients with R/R HL who are ineligible for ASCT: A Germany and United Kingdom retrospective study

Median PFS



Median PFS from initiation of BV: 15.1 months (95% CI, 8.9–22.0 months) with 52.1% progression free at 12 months

Median OS



Median OS from initiation of BV: 17.8 months (95% CI, 13.7–33.5 months) with 68.2% alive at 12 months

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; CI, confidence intervals; OS, overall survival; PFS, progression-free survival; R/R HL, relapsed or refractory Hodgkin lymphoma.

Bröckelmann PJ, et al. *Eur J Haematol* 2017;99:553–558.

Brentuximab vedotin in patients with R/R HL who are ineligible for ASCT: A Germany and United Kingdom retrospective study[1]

Safety*

- Documented incidence of peripheral neuropathy during BV treatment was 9.6%, of which 92.3% were non-serious

Summary

- The ORR (74.3%) was similar to previous retrospective studies (71% and 75%)[2,3]
- Results suggest that BV demonstrates real-world clinical effectiveness for patients with R/R HL who are ineligible for ASCT; a population where there is great clinical need and currently limited treatment options and poor outcomes

Adverse events of any grade occurring during treatment with BV

Events during regimen, n (%)	Germany N=78	UK N=58	All countries N=136
Leukopenia	8 (10.3)	9 (15.5)	17 (12.5)
Anaemia	8 (10.3)	4 (6.9)	12 (8.8)
Diarrhoea	5 (6.4)	2 (3.4)	7 (5.1)
Peripheral neuropathy	5 (6.4)	8 (13.8)	13 (9.6)
Nausea/vomiting	4 (5.1)	1 (1.7)	5 (3.7)
Thrombocytopenia	3 (3.8)	3 (5.2)	6 (4.4)

*The retrospective nature of the study and data derived from real-world patient files rather than study documentation makes it possible that AEs were underreported.

AEs, adverse events; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; ORR, objective response rate; R/R HL, relapsed or refractory Hodgkin lymphoma.

1. Bröckelmann PJ, et al. *Eur J Haematol* 2017;99:553–558; 2. Sasse S, et al. *Leuk Lymphoma* 2013;54:2144–2148; 3. Viviani S, et al. *Haematalogica* 2015;100:2.

NOVIGATE

Summary: Use of brentuximab vedotin in the R/R HL second salvage setting

- In a UK retrospective multicentre study of 99 patients with R/R HL, BV provided an ORR of 56% in a high-risk population, enabling a large proportion of patients to proceed to SCT either directly or following further treatment[1]
  - BV was judged to be relatively non-toxic in this real world setting in ASCT naïve R/R HL patients[1]
- In a retrospective real-world study of 136 patients from Germany and the UK, patients who were ineligible for ASCT demonstrated an ORR of 74% with median PFS of 15.1 months and median OS of 17.8 months following BV[2]
  - BV demonstrates real-world clinical effectiveness for patients with R/R HL who are ineligible for ASCT[2]

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R HL, relapsed or refractory Hodgkin lymphoma; SCT, stem cell transplant.

1. Eyre T, et al. *Br J Haematol*. 2017;179:471–479; 2. Bröckelmann PJ, et al. *Eur J Haematol* 2017;99:553–558.

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Please refer to the summary of product characteristics for details on the full side-effect profile and drug interactions of brentuximab vedotin. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Takeda UK Ltd. on 01628 537900

NAVIGATE

Abbreviated Prescribing Information:

Adcetris▼ (brentuximab vedotin)

(Refer to Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 50 mg powder for concentrate for solution for infusion. **Indication:** treatment of adult patients with relapsed or refractory (R/R) CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; treatment of adult patients with R/R systemic anaplastic large cell lymphoma (sALCL); treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy. **Dosage & Administration:** Administration should be under the supervision of a physician experienced in the use of anti-cancer agents. Recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks (If the patient's weight is more than 100 kg, the dose calculation should use 100kg). Recommended starting dose for retreatment of patients with R/R HL or sALCL who have previously responded to treatment with Adcetris is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks or at the last tolerated dose. Recommended starting dose in patients with hepatic impairment or severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Continue treatment until disease progression or unacceptable toxicity. Patients with R/R HL or sALCL who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles. Patients with HL at increased risk of relapse or progression following ASCT, should start treatment following recovery from ASCT. These patients should receive up to 16 cycles. Patients with CTCL should receive up to 16 cycles. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored during and after infusion. **Dose Adjustments:** If neutropenia develops during treatment it should be managed by dose delays. If peripheral sensory or motor neuropathy emerges or worsens during treatment patients may require delay and dose reduction or discontinuation of Adcetris. *Elderly patients (≥65yrs):* dosing recommendations for patients aged 65 and older are the same as for adults. *Paediatric patients (<18 yrs): S*afety and efficacy has not yet been established. In nonclinical studies thymus depletion has been observed. **Contraindications:** Hypersensitivity to the active substance or excipients. Combined use of bleomycin and Adcetris causes pulmonary toxicity. **Warnings and Precautions:** Progressive multifocal leukoencephalopathy (PML) has been reported in patients who received Adcetris after receiving multiple prior chemotherapy regimens; patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Adcetris dosing should be held for any suspected case of PML and permanently discontinued if a diagnosis of PML is confirmed. Acute pancreatitis has been observed in patients treated with Adcetris. Patients should be monitored for abdominal pain suggestive of acute pancreatitis. Adcetris dosing should be held if acute pancreatitis is suspected and permanently discontinued if a diagnosis is confirmed. Pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported in patients receiving Adcetris. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation is required and patients treated appropriately. Consider holding Adcetris dosing during evaluation and until symptomatic improvement. Serious and opportunistic infections have been reported in patients treated with Adcetris. Patients should be carefully monitored during treatment. Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. Monitor patients during and after infusion. Adcetris should be immediately and permanently discontinued if anaphylactic reaction occurs. Infusion should be interrupted if IRR occurs and appropriate management instituted. Infusion may be restarted at slower rate after resolution. Use premedication for subsequent infusions in instances of prior IRR. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome; these patients should be monitored and managed according to best medical practice. Adcetris may cause peripheral neuropathy which is reversible in most cases. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require delay and dose reduction or discontinuation of Adcetris. Refer to SmPC for dose adjustments if peripheral neuropathy develops. Grade 3 or 4 anaemia, thrombocytopenia and neutropenia can occur with Adcetris. Refer to SmPC for dose adjustments if neutropenia develops. Patients should be monitored for fever and managed according to best medical practice if febrile neutropenia develops. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with Adcetris with fatal outcomes. If SJS or TEN occurs, treatment with Adcetris should be discontinued and appropriate medical therapy administered. Gastrointestinal complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in the form of hepatotoxicity, has been reported. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Liver function should be tested before initiating the treatment and routinely monitored in patients receiving Adcetris. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of Adcetris. Any patient who experiences an event of hyperglycaemia should have their serum glucose monitored and managed appropriately. Monomethyl auristatin E (MMAE) clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations. The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. Adcetris should be used with caution in other CD30+ CTCL patients after consideration of the potential benefit-risk. Adcetris contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. **Pregnancy & lactation**: Women of childbearing potential should be using two methods of effective contraception during treatment with Adcetris and until 6 months after treatment. There are no data from the use of Adcetris in pregnant women. Animal studies have shown reproductive toxicity. There are no data as to whether Adcetris or its metabolites are excreted in human milk. **Fertility:** In non-clinical studies, Adcetris treatment has resulted in testicular toxicity, and may alter male fertility. Men being treated with Adcetris are advised not to father a child during treatment and for up to 6 months following the last dose. **Drug Interactions:** Co-administration of Adcetris: with strong CYP3A4 and P-gp inhibitors, such as ketoconazole, may increase the incidence of neutropenia; with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to Adcetris however, it appeared to reduce plasma concentrations of MMAE metabolites. Adcetris is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes e.g. midazolam. **Adverse Effects:** *Very common (≥10%):* Infection, upper respiratory tract infection, neutropenia, peripheral sensory neuropathy, peripheral motor neuropathy, cough, dyspnoea, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, pruritus, myalgia, arthralgia, fatigue, pyrexia, infusion-related reactions, weight decreased. *Common (≥1/100 to <1/10):* Herpes zoster, pneumonia, herpes simplex, oral candidiasis, anaemia, thrombocytopenia, hyperglycaemia, dizziness, alanine aminotransferase/ aspartate aminotransferase (ALT/AST) increased, alopecia, back pain, chills. *Uncommon (≥1/1000 to <1/100):* Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, tumour lysis syndrome, demyelinating polyneuropathy, pancreatitis acute, cytomegalovirus infection or reactivation, sepsis/ septic shock, febrile neutropenia, anaphylactic reaction, Stevens-Johnson syndrome/toxic epidermal necrolysis. *Frequency not known (cannot be estimated from the available data)*: Progressive multifocal leukoencephalopathy . Refer to the SmPC for details on full side effect profile and interactions. **Pharmaceutical Precautions:** Store vial in a refrigerator (2°C-8°C), protected from light. After reconstitution/dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C. **PI Date of Preparation:** January 2018. **PI approval code:** UK/ADC/1606/0038(3) **Legal category:** POM **Basic NHS Price & Marketing Authorisation:** £2,500 for each Adcetris 50mg vial (EU/1/12/794/001). **Further information is available from:** Takeda UK Ltd. Building 3, Glory Park, Glory Park Avenue, Wooburn Green, Buckinghamshire, HP10 0DF. Tel: 01628 537900 Fax: 01628 526617. Adcetris® is a registered trademark.

Adcetris has received a conditional marketing authorisation in Europe. A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required. The European regulatory agency will review new information on Adcetris at least every year and the summary of product characteristics will be updated as necessary.

Please refer to the summary of product characteristics for details on the full side-effect profile and drug interactions of Adcetris. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Takeda UK Ltd 01628-537900