Cost-effectiveness of brentuximab vedotin (Adcetris®) for the treatment of adult patients with CD30+ Hodgkin lymphoma at increased risk of relapse or progression following autologous stem cell transplant

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of brentuximab vedotin (Adcetris®)**.** Following assessment of the Applicant's submission, the NCPE recommends that brentuximab vedotin (Adcetris®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Takeda Products Ireland Ltd.) Health Technology Assessment dossier on brentuximab vedotin (Adcetris®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **October 2021**

Summary

In December 2020, Takeda Products Ireland Limited, submitted a dossier detailing the clinical effectiveness, cost effectiveness and potential budget impact of brentuximab vedotin for the treatment of adult patients with CD30+ Hodgkin lymphoma (HL) at increased risk of relapse or progression following autologous stem cell transplant (ASCT). It is a consolidation therapy. Reimbursement of brentuximab vedotin is sought on the Oncology Drug Management System.

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex. MMAE is subsequently released within the cell, binds to tubulin and induces cell arrest.

Brentuximab vedotin is administered by intravenous (IV) infusion at a dose of 1.8mg/kg (max dose 180mg) once every three weeks. Treatment should start following recovery from ASCT based on clinical judgement. Patients should receive up to 16 three-week cycles.

There are currently no other licensed treatments for consolidation therapy after ASCT in CD30+ HL. As such the only comparator is the current standard of care (SoC) referred to as watchful waiting.

1. Comparative effectiveness of brentuximab vedotin

The clinical efficacy of brentuximab vedotin was examined in AETHERA, a phase III double-blind, randomised, placebo-controlled trial in patients with CD30+ HL. The trial was conducted in North America and Europe. Patients were at high risk of relapse or progression after ASCT as indicated by at least one of the following risk factors: primary refractory HL, relapsed HL with an initial remission duration of less than 12 months or extranodal involvement at the time of pre-ASCT relapse. Patients were randomised to receive brentuximab vedotin IV 1.8mg/kg once every three weeks (n=165) or placebo IV once every three weeks (n=164). The Review Group consider the placebo arm to be an appropriate proxy for the SoC. Patients who experienced progression during the trial could

receive subsequent therapy with brentuximab vedotin or other therapies. A high proportion of patients in the placebo arm (47%) received brentuximab vedotin after progression.

Patient characteristics were generally balanced between arms. The primary efficacy endpoint was progression-free survival (PFS) as assessed by an independent review facility (IRF). Key secondary endpoints included overall survival (OS) and PFS by investigator (INV) assessment.

For the two-year primary analysis median PFS as assessed by IRF in the intent-to-treat (ITT) population was 42.9 months (95% CI 30.4 to 42.9) in the brentuximab vedotin arm compared with 24.1 months (95% CI 11.5 to not estimable) with placebo. The stratified hazard ratio (HR) for the primary analysis was 0.57 (95% CI 0.4 to 0.8). It appears that most of the PFS benefit is obtained in the first months after start of treatment, with a rapid increase in events in the placebo arm in the first six months of treatment and less steep PFS Kaplan-Meier curves after that time point in both arms. Three-year results for PFS per IRF were broadly in line with the two-year data. The majority of patients had no radiographic assessments after the last protocol mandated CT scan at 24 months, and were therefore censored for further analysis of PFS by IRF.

The two-year median PFS by INV assessment in the ITT population was not reached in the brentuximab vedotin arm (95% CI 26.4 to not estimable) compared with 15.8 months (95% CI 8.5 to not estimable) with placebo. The estimated 24-month PFS rate was 65% vs 45% for brentuximab vedotin and placebo respectively. The stratified hazard ratio was 0.50 (95% CI 0.36 to 0.70). Discordant outcomes between IRF and INV assessments were seen for 11% of assessments in the brentuximab vedotin arm and 15% in the placebo arm. Three and five year results for PFS by INV assessment were broadly in line with the two-year data. The improvement in PFS is considered to be clinically meaningful given that the literature and clinical opinion suggests that the majority of patients who do not relapse within two years of ASCT are in long-term remission.

OS results at primary analysis were very immature due to the limited number of events; interim two-year data showed no significant difference between treatment groups (HR 1.15; 95% CI 0.67 to 1.97). A total of 28 patients (17%) in the brentuximab vedotin arm and 25 patients (15%) in the placebo arm had died, and the estimated 24-month OS rate was 88% (brentuximab vedotin) compared with 89% (placebo). At five years, deaths between the arms did not show any considerable difference, with 40 and 37 deaths reported in the brentuximab vedotin and placebo arms, respectively. Post-relapse treatments in AETHERA are not reflective of clinical practice in Ireland. OS estimates are also likely to be confounded by the high proportion of treatment cross-over in the placebo arm after progression. A higher proportion of patients in the placebo arm received subsequent allogeneic stem cell transplant than in the brentuximab vedotin arm. The long-term OS benefit of brentuximab vedotin is unknown.

2. Safety of brentuximab vedotin

The safety profile of brentuximab vedotin was derived from the two-year primary data of AETHERA. Dose reductions due to adverse events (AEs) were recorded in 53 (32%) patients in the brentuximab vedotin group compared with four (3%) patients in the placebo group.

Overall, 98% of patients in the brentuximab vedotin arm and 89% in the placebo arm experienced a treatment-emergent adverse event (TEAE). The most frequent TEAEs of any grade, reported in the brentuximab vedotin vs placebo arms were; peripheral sensory neuropathy (56% vs 16%), neutropenia (35% vs 12%), upper respiratory tract infection (26% vs 23%), fatigue (24% vs 18%), peripheral motor neuropathy (23% vs 2%), nausea (22% vs 8%), and cough (21% vs 16%). Fifty-six percent of patients in the brentuximab vedotin arm and 32% in the placebo arm experienced TEAEs of grade 3 or above. The most common grade 3 or above TEAEs in the brentuximab vedotin vs placebo arms were neutropenia (29% vs 10%), peripheral sensory neuropathy (10% vs 1%) and peripheral motor neuropathy (6% vs 1%). Peripheral neuropathy led to discontinuation of brentuximab vedotin treatment in 38 (23%) patients and required dose modification (dose reduction or delay) in 51 (31%) patients. After two-years of follow-up the majority of patients had improvement or resolution in peripheral neuropathy symptoms.

In summary, higher percentages of TEAE and dose reductions due to AEs were observed in the brentuximab vedotin arm. However, the safety profile was consistent with the known safety information from the use of brentuximab vedotin in the previously approved HL and systemic anaplastic large-cell lymphoma indications.

3. Cost effectiveness of brentuximab vedotin

A de novo cost-effectiveness model was presented which consisted of a Markov component (to reflect costs and effects following ASCT and prior to relapse) and a partitioned survival analysis component (to reflect costs and effects after relapse). The cycle length was one week. The patient-starting age was 34.6 years and the model had a lifetime horizon (implemented as 75 years). Patient characteristics were derived from AETHERA and are in line with the population for which the treatment is licensed (i.e. patients at increased risk of relapse or progression following ASCT).

The Review Group were concerned with a structural assumption in the model which resulted in PFS being a surrogate marker for OS. This assumption results in a considerable quality-adjusted life year (QALY) gain for brentuximab vedotin vs the SoC despite the fact that there is no clinical evidence of OS benefit when brentuximab vedotin is used as a consolidation therapy post-ASCT. The Review Group considered scenarios where all the QALY gain post-relapse for brentuximab is removed, as a conservative proxy for an assumption of no survival benefit compared to SoC. Other concerns included the use of INV assessed time-to-progression (TTP) data from AETHERA, to model the duration of time a patient spent in the pre-relapse health state, which may have been biased in favour of the intervention. Also, there is a lack of robust evidence to inform outcomes in relapsed/refractory setting after failure of ASCT. The Review Group also noted that the majority (77%) of the incremental QALY gain occurs after ten years where treatment benefit is very uncertain. By contrast, 99% of incremental costs are incurred during the first five years.

The deterministic incremental cost-effectiveness ratio (ICER) generated under the Applicant's base case assumptions are shown in Table 1.

Table 1 Applicant's base case results (deterministic)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Brentuximab vedotin	162,897	11.77	-	-	-
Standard of care	91,919	9.44	70,978	2.33	30,524

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year
Figures in the table are rounded, and so calculations may not be directly replicable.

Although the PFS benefit is noted, the Review Group have reservations in relation to the Applicant's base case ICER. The ICER presented by the Applicant assumes an OS benefit for brentuximab that has not been demonstrated in the clinical trial, and thus represents an optimistic scenario regarding the cost-effectiveness. The Review Group have not presented an adjusted base case as removing the assumption of surrogacy between PFS and OS in the model would have required modelling changes outside the scope of the NCPE assessment. However, the Review Group did consider scenarios where post-relapse survival benefit with brentuximab vedotin was removed; the ICER was less than €80,000 per QALY in the most extreme scenario where patients died immediately upon relapse.

The probabilistic ICER for brentuximab vedotin vs SoC was similar to the deterministic ICER. The probability of cost effectiveness, at a cost-effectiveness threshold of €45,000 per QALY is 78%, and at a threshold of €20,000 per QALY is 10%. The Review Group considered that the probabilistic analysis (PSA) failed to capture the uncertainty associated with the cost-effectiveness results because the key uncertainties in the model were structural. A further major limitation of the PSA is that the majority of parameters affecting post-relapse outcomes and costs are not varied in the PSA, despite these parameters being highly uncertain.

4. Budget impact of brentuximab vedotin

The price to wholesaler for brentuximab vedotin 50mg powder for concentrate for solution for infusion is €3,072.36 per vial. The total drug cost per consolidation course of brentuximab vedotin excluding administration fees is €98,358 excluding VAT (€122,297 including VAT). This cost accounts for the relative dose intensity and the mean number of cycles (12) received by patients in AETHERA as well as vial sharing assumptions.

The Applicant estimated the five-year cumulative gross budget impact to be €4.48 million. This estimate assumes that 50% patients who receive ASCT are considered at high-risk of relapse or progression, and was based on five patients receiving treatment in Year 1 rising to eight patients in Year 5. The Applicant assumes that brentuximab vedotin will replace SoC which does not include any drug treatment for patients until they relapse. As such the net drug budget impact is equal to the gross budget impact. The Review Group presented an alternative scenario, based on clinical opinion, where most patients who receive ASCT could be considered at high-risk of relapse and eligible for brentuximab vedotin. In this scenario the five-year budget impact is €8.96 million; the Review Group consider this an upper bound of the potential budget impact of brentuximab vedotin for this indication.

5. Patient submissions.

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

The NCPE recommends that brentuximab vedotin be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

** This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medicinal Goods) Act 2013.*