



**Cost–effectiveness of brentuximab vedotin (Adcetris®) for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed at least one autologous stem cell transplant.**

The NCPE has issued a recommendation regarding the cost-effectiveness of brentuximab vedotin (Adcetris®) for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed at least one autologous stem cell transplant. The NCPE does not recommend reimbursement of brentuximab (Adcetris®) at the current price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturer's (Takeda) economic dossier on the cost-effectiveness of brentuximab vedotin (Adcetris®) in the treatment of relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed at least one autologous stem cell transplant. 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 examine 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, such as brentuximab, 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.

Brentuximab vedotin (Adcetris®) is currently indicated for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin Lymphoma following: (1) autologous stem cell transplant (ASCT) or (2) at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Brentuximab is also indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma. In January 2013, Takeda were requested to prepare a full pharmacoeconomic submission for the NCPE. The NCPE received a submission on 16<sup>th</sup> September 2013 on the cost-effectiveness of brentuximab for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed at least one ASCT. Additional information was requested on 31<sup>st</sup> October 2013. All requested data and the final submission document were provided to the NCPE by 7<sup>th</sup> March 2014. The cost-effectiveness of brentuximab for systemic anaplastic large cell lymphoma was not evaluated.

Brentuximab is an antibody drug conjugate that is specifically targeted against the tumour necrosis factor receptor CD30 which is expressed on the surface of tumour cells in haematological malignancies including Hodgkin Lymphoma and systemic anaplastic large cell lymphoma. In January 2009, brentuximab was designated as an orphan medicinal product for both Hodgkin Lymphoma and systemic anaplastic large cell lymphoma and the drug received conditional European marketing authorisation on 25<sup>th</sup> October 2012.

1. The economic model evaluates brentuximab in patients with relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed chemotherapy and at least one prior ASCT. There is no defined standard of care for those that relapse following ASCT and treatment tends to be highly individualised. A variety of standard treatment options are currently available and include: single and multi agent chemotherapy with/without radiotherapy (CTRT), intensive treatment strategies (second autografts, reduced intensity conditioning allogeneic stem cell transplant (alloSCT)) or drug development trials. The economic evaluation compared brentuximab with (1) CTRT and (2) CTRT with intention to alloSCT.
2. The safety and efficacy of brentuximab was evaluated in a pivotal phase II, multinational, single-arm, non-randomised, open-label trial (SG035-0003 study, Younes *et al.* 2012). The sample included patients (n=102) who had relapsed after ASCT, was relatively young (median age 31 years) and was heavily pre-treated (median 3.5 prior chemotherapy regimes). The primary outcome was objective response rate as assessed by independent review facility. Secondary

outcomes included progression free survival (PFS) and overall survival (OS) assessed by independent review facility. Assessment of efficacy by study investigators was collected as a protocol-defined, exploratory analysis. Health related quality of life was not included as an outcome measure.

3. An independently-assessed objective response rate of 75% was achieved (complete response 34%, and partial response 40%). After a median observation time of 18.5 months, 30% of patients were alive without disease progression and 27% had died; the remainder had progressive disease. The most recent data based on a median follow-up of 32.7 months, reports a median PFS and OS of 5.6 months and 40.5 months respectively, with an estimated 36 month survival rate of 54%. In the company submission, incremental cost-effectiveness analyses using independently-assessed and investigator-assessed PFS and OS data was conducted and the investigator-assessed data was presented for the base case. The Review Group consider the independently-assessed data to be more robust and appropriate for the base case analysis. The SG035-0003 trial clearly demonstrates the impact of independent review on PFS estimates: PFS by independent review 24.4 weeks (95%CI 21.9, 39.1) and by investigator 40.4 weeks (95%CI 30.7, 53.1). Efficacy data for the comparators were derived from observational studies identified from a targeted systematic review performed by the company.
4. The SG035-0003 study was a single-arm, non-comparative study. There is therefore no direct evidence of efficacy relative to the comparators. Data from the observational study conducted by Robinson *et al.* (follow-up 5.2 years) was used to estimate PFS for the alloSCT comparator. PFS in the subset of patients who had received at least one prior post-ASCT systemic therapy in the 003-trial was used to estimate PFS for the CTRT comparator. An observational study by Martinez *et al.* was used to estimate OS for both comparators.
5. Beyond the period of the clinical trial/observational data (~3 years), PFS for brentuximab and CTRT was assumed to be equal to the alloSCT comparator for a further 2.2 years. Thereafter the model assumes that all comparators have the same constant risk of progression (hazard ratio of 1.0 assumed). OS with brentuximab was also assumed to be associated with a hazard ratio of 1.0 compared to the weighted hazard of CTRT and alloSCT. The review group had concerns about the extrapolation of PFS beyond the trial periods for the base case analysis. This was due to the fact that the data were coming from different

trials and the models used had poor statistical fit. The assumption of equal hazard was of concern since it implies the protective effect of the intervention is of indefinite duration.

6. The most commonly reported treatment related adverse events reported in the pivotal phase II trial were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%) and neutropenia (19%). Adverse events leading to treatment withdrawal occurred in 20% of patients. Dose reduction occurred in 11% of patients, mostly as a result of peripheral neuropathy.
7. A three-state Markov model, incorporating progression-free survival (PFS), progressive disease and death was used to perform a cost-utility analysis. The model estimated the cost-effectiveness of brentuximab over a period of 40 years from a healthcare payer perspective and the standard discount rate of 4% for costs and benefits was applied. Utility data were derived from a time trade off study of the UK general population (n=100).
8. Separate scenarios were submitted using independently-assessed and investigator-assessed PFS and OS data. The NCPE review group considered the results of the economic model based on the independently-assessed outcomes to be more appropriate than the investigator-assessed outcomes. For the alloSCT ineligible population, the relevant comparator is CTRT. For the alloSCT eligible population, an incremental analysis including brentuximab, CTRT with intent to alloSCT, and CTRT alone, results in CTRT with intent to alloSCT being extendedly dominated by brentuximab and CTRT. Therefore, the relevant comparator in this population is also CTRT. Comparison of brentuximab to CTRT, using independently-assessed outcomes, results in an incremental cost of €85,786 and a QALY gain of 1.10. This yields an ICER of €78,106/QALY.
9. The company presented a number of scenarios, a one way sensitivity analysis as well as a probabilistic analysis in order to explore uncertainty associated with the parameters. One-way sensitivity analysis highlights that the model is highly sensitive to PFS and OS estimates, inclusion of the cost of alloSCT for the proportion of patients in the brentuximab arm that receive alloSCT and the time horizon. Alternative assumptions for these parameters, based on independently-assessed outcomes, result in ICERs which vary between €99,858/QALY and €148,729/QALY. When a five-year time-horizon is adopted the ICER increases to €131,870/QALY. This scenario is likely to robustly reflect the benefit of the

drug on the basis of the evidence available, without relying on extrapolations about which there is substantial uncertainty. The probabilistic analysis indicates that at a threshold of €45,000/QALY, the probability of brentuximab being cost effective is 1%.

10. The Review Group has a number of concerns with the comparative effectiveness data included in the company submission including the lack of comparative efficacy data for brentuximab compared to standard of care and the inherent bias associated with comparing across individual trial arms; use of investigator reported data from the pivotal phase II trial for the company analysis; limited evidence of effectiveness for the comparators and the high level of uncertainty of the results of the model to the assumptions about PFS and OS. There is currently no direct evidence to demonstrate an OS benefit of brentuximab versus standard of care and there is no evidence that brentuximab leads to an improvement in quality of life.
11. The projected number of patients with relapsed or refractory CD30 positive Hodgkin Lymphoma who are eligible for treatment is 10 per year (5 post ASCT and 5 ASCT ineligible) and it is assumed that this number will remain stable over time; thus a total of 50 patients over a period of 5 years may be treated for relapsed or refractory CD30 positive Hodgkin Lymphoma. The cost of brentuximab per patient per year is estimated at €114,620 (including 23% VAT). This cost assumes that partially used vials will be discarded and uses the regimen and mean duration of therapy (9.7 cycles and relative dose intensity of 93.5%) reported in the SG035-0003 trial. The gross budget impact is estimated at €1,106,032 per year (€659,729 post ASCT and €446,304 ASCT ineligible); the cumulative 5 year budget impact is estimated at €5,530,162. The net budget impact, taking into account cost offsets, is €672,510 per year (€322,213 post ASCT and €350,297 ASCT ineligible); the cumulative 5 year net budget impact is €3,362,550. A budget impact analysis for the indication of systemic anaplastic large cell lymphoma was not included in the company submission. However, it is estimated that approximately 3-4 patients per year would be eligible for treatment.
12. Brentuximab is the first agent approved for the treatment of Hodgkin Lymphoma in nearly three decades and the first agent specifically indicated to treat systemic anaplastic large cell lymphoma. To date, impressive initial response rates have been demonstrated with brentuximab for patients with relapsed or refractory

CD30 positive Hodgkin Lymphoma with limited treatment options and no definite standard of care. However, there is currently no direct evidence to demonstrate a superior survival rate or an improvement in quality of life over current standard of care.

At its current price, brentuximab cannot be recommended as a cost-effective treatment option for adult patients with patients, with relapsed or refractory CD30 positive Hodgkin Lymphoma who have failed at least one ASCT. The calculated ICERs, exceed the usual willingness to pay threshold for pharmaceuticals. Furthermore, there is high uncertainty associated with these ICERs, in particular regarding PFS and OS, which may result in ICERs exceeding €130,000/QALY.

The cost-effectiveness of brentuximab vedotin in patients with relapsed or refractory CD30 positive Hodgkin Lymphoma that are ineligible for ASCT, or for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, was not evaluated.