Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Brentuximab vedotin

Proprietary Product Name: Adcetris

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

September 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ABMTRS	Australasian Bone Marrow Transplant Recipient Society
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine combination therapy
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
ASA	Australian-specific annex
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibodies
AusPAR	Australian Public Assessment Report
AVD	Doxorubicin, vinblastine, and dacarbazine combination therapy
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone combination therapy
BrECADD	Brentuximab vedotin plus etoposide, adriamycin, cyclophosphamide, dacarbazine, and dexamethasone combination therapy
BrECAPP	Brentuximab vedotin plus etoposide, adriamycin, cyclophosphamide, procarbazine, and prednisone combination therapy
BSC	Best supportive care
CFR	Code of Federal Regulations
CH-P	Cyclophosphamide, doxorubicin, and prednisone combination therapy

Abbreviation	Meaning
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone combination therapy
CI	Confidence interval
CMHP	Committee for Medicinal Products for Human Use
CMI	Consumer Medicine Information
CR	Complete response
CR/CRu	Complete remission rate
CrCl	Creatinine clearance
CRR	Complete response rate
CSF	Colony-stimulating factors
CSR	Clinical Study Report
CT	Computerised tomography
DHAP	Dexamethasone/high-dose Ara-C/cisplatin
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life (EuroQol) 5 dimensional 3 level
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GHSG	German Hodgkin Study Group
GSDB	Global Safety Database
HL	Hodgkin lymphoma

Abbreviation	Meaning
HLT	High Level Term
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplantation
ICE	Ifosfamide/carboplatin/etoposide
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IGEV	Ifosfamide/gemcitabine/vinorelbine
IgG1	Immunoglobulin G1 isotype
IRR	Infusion-related reaction
IV	Intravenous
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board (Netherlands)
MMAE	Monomethyl auristatin E
ORR	Objective response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PI	Product Information
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTCL	Peripheral T-cell lymphoma
QoL	Quality of life
r/r HL	Relapsed or refractory Hodgkin lymphoma

Abbreviation	Meaning
RMP	Risk Management Plan
SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SD	Stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TNFR	Tumour necrosis factor receptor
TTNT	Time to next treatment

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	15 September 2016
Date of entry onto ARTG	20 September 2016
Active ingredient(s):	Brentuximab vedotin
Product name(s):	Adcetris
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd 2-4 Lyon park Road, Macquarie Park NSW 2113
Dose form(s):	Powder for injection
Strength(s):	50 mg
Container(s):	Glass vial
Pack size(s):	1 x 50 mg vial
Approved therapeutic use:	*Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT (see 'Clinical Trials').*
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The 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 100 kg (see Table 10 in 'Determining dosage amount' [in Attachment 1])
ARTG number (s):	203372

Product background

This AusPAR describes the application by the sponsor to register Adcetris (brentuximab vedotin), indicated for the:

> *'Treatment of patients with CD 30+ Hodgkin Lymphoma (HL) who are at risk of relapse or progression following autologous stem cell transplant (ASCT).'*

Treatment of HL varies according to staging and risk stratification at diagnosis. Staging is according to the number and location of lymph node involvement, bulk, presence of extra-nodal disease and B symptoms. Unfavourable risk factors include age (> 40 to 50 years), presence of extra-nodal or bulky disease, presence of B symptoms or elevated erythrocyte sedimentation rate (ESR), low albumin (< 4 g/dL) or anaemia or leucocytosis.

The response to current frontline therapy results in a curative outcome for approximately 90% of patients with classical disease and 30% for those with disseminated disease.

For those 10% to 20% of patients with HL who do not respond to frontline therapy or who relapse following an initial response to frontline therapy (r/r HL), the treatment of choice consists of high-dose 'salvage' chemotherapy followed by ASCT.

Salvage chemotherapy regimens such as dexamethasone/high-dose Ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and determine eligibility for ASCT. Patients with significant organ disease, poor performance status or lack of response to salvage therapy are usually not considered eligible for ASCT.

Up to 50% of patients treated with ASCT may relapse following this therapy or not respond.

Risk factors for progression following ASCT have been extensively studied to identify patients most likely to benefit from ASCT. Pre-ASCT risk factors consistently reported to be associated with relapse or refractory disease post-ASCT include primary refractory Hodgkin's lymphoma, initial remission duration of less than 12 months, Ann Arbor stage III or IV at relapse, presence of extra-nodal or advanced-stage disease at time of relapse, presence of B symptoms, lack of response to pre- transplantation salvage chemotherapy, and residual disease pre-ASCT (defined by computerised tomography (CT) or positron emission tomography (PET) scans).

A variety of prognostic indices have been proposed but no universal agreement has been reached. These indices commonly divide patients into low, intermediate or high risk groups according to the number of risk factors present (for example, 0 or 1, 2, 3 or more risk factors respectively). The 5 year progression-free survival (PFS) rate for patients identified by different prognostic indexes is approximately: 65% to 80% for low risk, 25% to 40% for moderate risk and 10% to 20% for high risk. The 5 year overall survival (OS) for patients has been variably reported as 80 to 100% for low risk, 55% to 85% for intermediate risk and 13% to 57% for high risk.

Brentuximab vedotin is an anti-neoplastic agent active against CD30-expressing cells. It comprises a CD-30 directed antibody-drug conjugate (ADC) consisting of three components: the chimeric immunoglobulin G1 isotype (IgG1) antibody cAC10, specific for human CD30; the microtubule disrupting agent, Monomethyl auristatin E (MMAE); and a protease-cleavable linker that covalently attaches MMAE to cAC10.

CD30 is a member of the tumour necrosis factor receptor (TNFR) and was originally described as a marker of Hodgkin's and Reed-Sternberg cells in Hodgkin's lymphoma. It may also be expressed on virus-infected lymphocytes and other neoplasms of lymphoid origin. In non-pathologic conditions, CD30 expression is generally restricted to activated B and T lymphocytes and NK cells with lower levels in activated monocytes and eosinophils. It is generally not detected on healthy tissue or resting lymphocytes.

Brentuximab vedotin was granted orphan drug designation for the treatment of relapsed or refractory HL and; systemic anaplastic large cell lymphoma (SALCL) on the 18 September 2012.

The current submission proposes the use of brentuximab vedotin as consolidation treatment post-ASCT for patients at risk of relapse as opposed to the current indication for patients with relapse post-ASCT.

As of July 2015, there are over 50 studies researching (active, recruiting or soon to start recruiting) the use of brentuximab vedotin in Hodgkin lymphoma registered at ClinicalTrials.gov. These studies are investigating the use of brentuximab vedotin at different stages of HL including frontline therapy or after first relapse; in different patient populations (over 60 years old and paediatric); in combination with other agents; in different roles (alternative to salvage chemotherapy prior to ASCT, and as adjuvant therapy post allogeneic stem cell transplant).

Regulatory status

The product was initially registered on the Australian Register of Therapeutic Goods (ARTG) on 20 December 2013. Similar submissions to this current Australian submission were under consideration or had been approved in the following countries or regions:

- *European Union (EU):* On 26 May 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending a change to the terms of the marketing authorisation. The proposed indication has not been formally adopted yet. The proposed additional indication is:

  'Adcetris is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.'

- *USA:* A supplement approval was completed with the Food and Drugs Administration on 4 March 2016 to include the indication:

  'Adcetris is a CD30-directed antibody-drug conjugate indicated for treatment of patients with:

  Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation'

- *Canada:* At the time of submission, an application was pending approval for:

  'The post-ASCT consolidation treatment of patients with HL at high risk of relapse or progression.'

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

No changes to the formulation were proposed with this submission.

Advice of the pharmaceutical sub-committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) was not sought for this submission.

III. Nonclinical findings

No new preclinical data was presented. There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

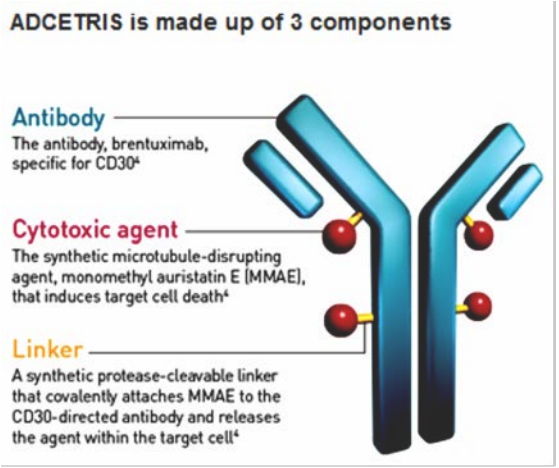
A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Brentuximab vedotin (Adcetris) is an anti-neoplastic agent that is active against CD30-expressing tumour cells. It is an antibody drug conjugate (ADC), with a structure as shown in Figure 1, below and consists of three components:

1. the chimeric IgG1 antibody cAC10, specific for the human cell membrane receptor CD30;
2. the micro-tubule disrupting agent MMAE that is covalently bound to the cAC10 moiety; by
3. a protease cleavable linker.

Figure 1. Schematic of brentuximab vedotin structure



The biological activity of the ADC is thought to result from a multi-step process that ends in apoptotic cell death of CD30-expressing cells. Efficacy of a regimen of brentuximab vedotin of 1.8 mg/kg every 3 weeks has been shown in patients with relapsed or refractory HL or sALCL.

The currently approved indications are:

- *'Treatment of adult patients with relapsed or refractory 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 relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)'*

The proposed extension of indications is a new Hodgkin Lymphoma indication:

- '*The treatment of patients with CD30+ Hodgkin Lymphoma at increased risk of relapse or progression following autologous stem cell transplant (ASCT).'*

Contents of the clinical dossier

- Clinical Overview
- One pivotal efficacy/safety study, Study SGN35-005:
  - Summary of Clinical Efficacy, Summary of Clinical Safety
  - One separate immunochemistry report for Study SGN35-005
- One Clinical Study Report (CSR) for Study35-008b

- Method validation reports for:
  - electrochemiluminescent method to detect antibodies to SGN-35 in human serum; and
  - determination of free MMAE in human sodium citrate plasma by HPLC with MS/MD detection.
- Five Periodic Safety Update Reports (PSURs), covering a period from August 2012 to August 2015

The following were provided for the second round evaluation:

- Clinical Study Report for SGN35-008b
- An additional PSUR covering the period August 2014 to August 2015
- Cumulative reviews for pulmonary toxicity and hepatotoxicity were provided in the Sponsor's Responses to Clinical Questions
- The Safety Related Request which included updated safety information for the two Phase II registrational studies for the currently approved indication and cumulative reviews for pulmonary toxicity, hepatotoxicity and gastrointestinal complications

Clinical rationale

The sponsor provided a brief background description that includes a discussion of risk factors for progressive disease following ASCT and a description of the pivotal study. The proposed new HL indication for use as adjuvant therapy in patients following ASCT for relapsed or refractory CD 30+ HL is based on the results of a Phase III randomised, double blinded, placebo controlled, 2 arm multicentre study in 329 patients at risk of relapse or progression following ASCT (Study SGN35-005, AETHERA). This study was designed so that treatment was initiated as early as possible post-ASCT, when acute toxicities have resolved and the lymphoma is at a minimal residual state. According to the sponsor's Clinical Overview, it is not possible to distinguish patients cured by ASCT alone from patients destined to relapse at this time (approximately 30 to 45 days post-ASCT) as residual masses on CT scans may continue to resolve over months and patients who appear to be in complete remission may have microscopic disease not measurable by radiographic scans. Pre-ASCT risk factors were therefore used to select patients at increased risk of progression.

A discussion of the involvement of regulatory authorities (including EMA, Netherlands' Medicines Evaluation Board (MEB), Paul Erlich Institute and the US (United States) Food and Drug Administration (FDA) in the development of design and protocol amendments of this study are provided in the sponsor's Clinical Overview. Brief descriptions of pre-submission discussions with the Netherlands' Medicines Evaluation Board, Paul Erlich Institute were also provided. The Netherlands MEB were reported to comment that: *'it was unsurprising that the interim analysis of the secondary OS endpoint did not show a survival difference due to the study design and the limited number of events but requested further explanation of these data, including the influence of crossover effects, in the dossier*'. The sponsor's Clinical Overview comments that: '*The clinical relevance of the PFS result in light of no OS improvement and the advantages of treating patients post-ASCT rather than within the licensed indication were discussed'* with the reported opinion of the Netherlands MEB that '*the importance of treating early and effectively when the tumour burden is low rather than waiting for relapse should be emphasised'* and that the MEB and Paul Erlich Institute were in agreement that there were no universal criteria to define patients at high risk of relapse or progression.

Brief descriptions of the discussions with the FDA were provided. There was agreement that the study data supported submission of a supplemental Biologics Licensing Application. It was noted that the FDA was concerned by the heterogeneity of the proposed patient population and the use of progression free survival as the primary endpoint and it did not agree that the study was a suitable confirmatory study for change from accelerated approval to regular approval.

For the first and second evaluations (including information from the sponsor's response to clinical questions) the rationale presented in the sponsor's Clinical Overview provides a description of HL, the use of ASCT, the poor prognosis of patients who relapse following ASCT for HL and a description of brentuximab vedotin and its potential role as adjuvant therapy for this group of patients. A description of the Phase III study and involvement of regulatory bodies in its design are provided. The rationale is adequate but was assessed to show some gaps in its discussion.

Patients at risk of developing refractory or relapsed HL following ASCT are presented as having an 'unmet need' due to poor prognosis and the lack of effective therapies. The sponsor's Clinical Overview offers 9 different pre-ASCT factors that may indicate at-risk patients and comments that no single factor can '*sufficiently identify every patient at increased risk of relapse*', although the more risk factors that are present the worse is the projected 5 year progression free survival rate. The sponsor's Clinical Overview does not provide a discussion, or an estimate, of the proportion of patients having ASCT for HL who would have one or more risk factors present.

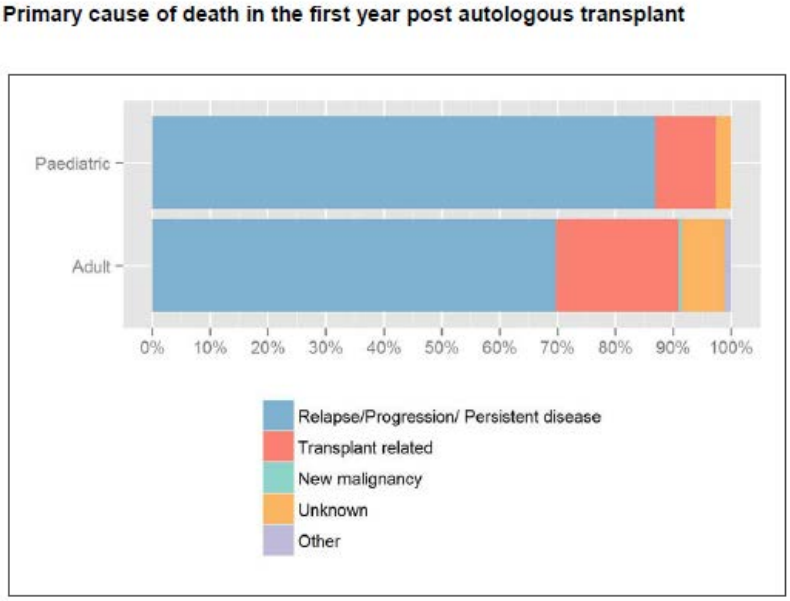
Estimated Australian population for the proposed usage

In response to a clinical question (see Attachment 2: Section 12, Question 3 'Estimated Australian Population' along with the sponsor's response) the sponsor has provide additional information regarding the use of ASCT for HL in Australia and New Zealand, citing the Australasian Bone Marrow Transplant Recipient Society (ABMTRS) Annual Data Summary 2014 as source.

The sponsor notes that the use of ASCT for HL has declined in recent years (from 95 in 2009 to 55 in 2014) and speculates that this is due to improved frontline therapies resulting in cures for more patients. In the source material, the evaluator notes that there were 60 patients in Australia and New Zealand who received ASCT for HL in 2014 (see Figure 2, below).[1] This source also provides data regarding cause of death in the first 12 months post-transplant for the years 1998 to 2013. This shows that for the patients who died within the first 12 months after ASCT around 20% of patients being treated with ASCT died from complications related to ASCT (a similar graphic for allogeneic transplants found transplant related mortality of around 60%) and around 70% of deaths were due to progressive disease.

[1] Australasian Bone Marrow Transplant Recipient Society Annual Data Summary 2014 provided by the sponsor.

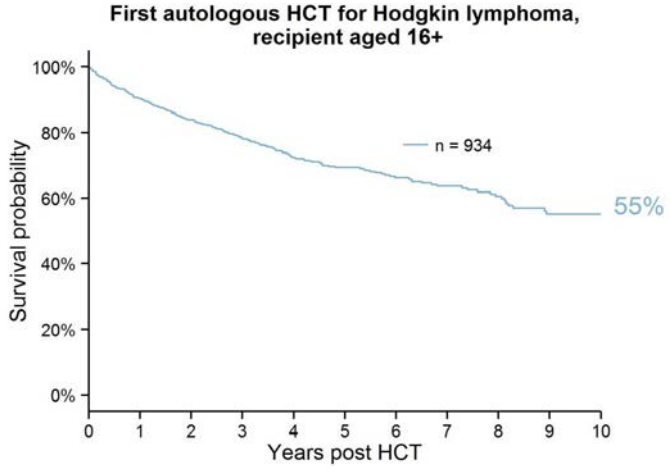
Figure 2. Primary cause of death in the first 12 months following ASCT in Australia between 1998 to 2013



Cause of death	Recipient 0-15		Recipient 16+		Total	
Disease relapse or progression	160	87.0%	1,377	69.7%	1,537	71.2%
Transplant related	19	10.3%	419	21.2%	438	20.3%
New malignancy	0	0.0%	11	0.6%	11	0.5%
Unknown	5	2.7%	146	7.4%	151	7.0%
Other	0	0.0%	22	1.1%	22	1.0%
Total deaths	**184**	**100%**	**1,975**	**100%**	**2,159**	**100%**

The ABMTRS 2014 summary also provided 10-year survival curves according to condition requiring ASCT. The curve for HL is shown below in Figure 3.

Figure 3. 10 Year survival curve for patients aged ≥ 16 years receiving ASCT for Hodgkin Lymphoma in Australia and New Zealand



This data indicates that around 55% of HL patients treated with ASCT in Australia are effectively cured of the disease.

The sponsor has provided an estimate of around 60% of patients who receive ASCT for HL in Australia had one or more risk factor(s) for relapse following ASCT. This estimate is

based on advice from clinicians on an Australian Advisory Board for Adcetris who estimated that 50% to 70% of patients had risk factors for progression post-ASCT. The sponsor took the mid-point of this estimate for the calculation. Using the annual number of patients receiving ASCT and the estimate of 60% of these having ≥ 1 risk factor for relapse. The sponsor has estimated that approximately 33 patients per year who would be suitable for treatment with brentuximab vedotin under the proposed indication in Australia.

Rescue or consolidative (adjuvant) therapy

The sponsor's Clinical Overview makes only brief reference to the impact of the product, as currently approved, when used as rescue therapy in patients who relapse after ASCT. It comments that the response achieved when used as rescue therapy is not '*curative*' and describes long-lasting complete remission in '*a small number*' of patients. It notes that references are available to indicate that brentuximab vedotin has been described "as a game changer" in patients with refractory or relapsed HL following ASCT and sALCL: '*Before the advent of brentuximab vedotin, both conditions had few therapeutic options, all of limited efficacy, and their prognosis was overall dismal'.*[2]

Brentuximab vedotin was approved for the indication of the treatment of relapsed or refractory HL in the USA in August 2011, in the EU in October 2012 and in Australia in December 2013. Despite this, the sponsor's Clinical Overview does not provide a discussion of the use of brentuximab vedotin as rescue therapy (the currently approved indication) compared to use as consolidative therapy (the proposed extension to indication). No reference, in this evaluation, was made to the results of the 3-year follow-up of the Phase II study that were first made publicly available in June 2013. These results can assist in the determination of any advantage in the use of brentuximab vedotin as adjuvant therapy compared to its currently approved use as 'rescue therapy'.

The sponsor has provided a discussion that addresses this question in response to a clinical question (see Attachment 2: Section 12, Question 4 'Consolidation versus rescue therapy' along with the sponsor's response). In this response, the sponsor argues that the use of brentuximab vedotin as consolidative therapy following ASCT in all patients at increased risk of relapse will result in fewer patients having to experience the potential trauma of HL recurrence and the poor prognosis consequent to this. The sponsor presents data that, according to PFS by investigator, approximately 55% of placebo patients in the pivotal study who were at increased risk of relapse were not cured by ASCT alone, as opposed to approximately 35% of patients receiving consolidation treatment with brentuximab vedotin. From this the sponsor concludes that consolidation therapy with brentuximab vedotin offers sustained progression-free survival and the potential for cure to approximately 20% more patients.

The clinical evaluator has two main concerns with this contention. Firstly, given the relatively brief duration of follow-up (median observation time of 30 months), it is not clear to the evaluator that the term 'cure' can be used. Longer follow-up is needed to determine if brentuximab vedotin as consolidative therapy following ASCT has resulted in cure or merely in a delay in relapse. Secondly, it is important to remember that historical data shows that around 50% of patients receiving ASCT for relapsed HL are effectively cured and that 45% of patients in the placebo arm of the pivotal study experienced sustained progression free survival from ASCT alone. If brentuximab vedotin is used as proposed, these patients would be exposed to the risks of brentuximab vedotin therapy without experiencing any benefit. The risks of brentuximab vedotin therapy are considerable, and include a number of reactions that have been associated with fatal outcome.

[2] Vaklavas C et al. Safety and efficacy of brentuximab vedotin in patients with Hodgkin lymphoma or systemic anaplastic large cell lymphoma. Ther Adv Hematol (2012) 3(4) 209–225.

To avoid exposing patients who would otherwise be cured by ASCT alone to these risks, it is necessary to identify the patients who will most benefit from consolidative therapy. If this cannot be done, and if the proposed usage is approved, it must be ensured that the risks are made explicit in the information provided to prescribers and consumers to enable informed prescribing and consent.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Study SGN35-005

The sponsor's Clinical Overview states that the study was conducted in accordance with Directive 2001/20/EC and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and FDA guidelines (Title 21 of the Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, 312; ICH E6).[3,4,5] A sample consent form, Clinical Study Report Approval form and Audit certificate (routine audits of 8 study sites and 4 service providers) were provided with the CSR.

Study SGN35-008b

The CSR states that the study was conducted in accordance with principles enunciated in the declaration, the ICH GCP, and applicable FDA regulations/guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic or pharmacodynamics information was submitted with this application except for a description of the incidence of anti-therapeutic antibodies (ATA) in Study SGN35-005 (AETHERA study) as described below and Study SGN35-008b describing pharmacokinetics in hepatic or renal impairment.

The pharmacokinetics and pharmacodynamics of brentuximab vedotin were presented to the TGA in a previous submission of brentuximab vedotin as a new clinical entity for the currently approved indications. This included: 2 Phase I dose escalation studies, one study to assess the effect of brentuximab on cardiac repolarisation and one study to investigate drug-drug interactions between brentuximab vedotin and substrates of CYP3A4 or modulators of CYP activity. Some limited pharmacology information was also provided by 2 Phase II studies.

A detailed evaluation of the pharmacokinetic and pharmacodynamic information provided previously can be found in Section VI: Overall conclusion and risk/benefit assessment of the Australian Public Assessment Report (AusPAR) for Brentuximab vedotin (Adcetris).[6]

[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
[4] CFR 21 Part 10: Electronic records and electronic signature related; Part 50: Protection of human subjects in clinical trials; Part 54: Financial Disclosure by Clinical Investigators, Part 316: Orphan Drug & the Orphan Drug Act 1983. US FDA
[5] ICH harmonised tripartite guideline guideline for good clinical practice E6(R1); Current Step 4 version dated 10 June 1996
[6] Section VI. Overall conclusion and risk/benefit assessment, Australian Public Assessment Report for brentuximab vedotin; Proprietary Product Name: Adcetris. Sponsor: Takeda Pharmaceuticals Australia Pty Ltd. Date of AusPAR May 2014. Therapeutic Goods Administration, Canberra.

Descriptions of the pharmacology of brentuximab vedotin can also be found in the European Public Assessment Report (EPAR) for the initial approval of brentuximab vedotin in the European Union (EU).[7]

Evaluator's conclusions on pharmacokinetics

The summary of pharmacokinetics provided above is largely based on the information provided in the previous AusPAR and EPAR for brentuximab vedotin to provide background for subsequent sections in this report.[8] The only new pharmacokinetic data submitted with was the incidence of ATA in Study SGN35-005, the pivotal efficacy and safety study provided for the proposed indication. Study SGN35-008b was provided by the sponsor upon request during the second round evaluation.

Study SGN35-008b was an open label, non-randomised, Phase I study that investigated the PK and adverse event profile of brentuximab vedotin in patients with hepatic or renal impairment, with comparison made to patients with normal renal and hepatic function. This study was limited by small numbers enrolled, even smaller numbers with all PK sampling performed, exclusion of patients requiring dialysis, lack of investigation of the effect of repeated dosing and use of a control arm that was receiving ketoconazole during the last 3 days of Cycle 1. However, within these limitations, it appears that both renal and hepatic impairment increases MMAE exposure in a way that is clinically meaningful, and that hepatic impairment has a more marked effect. This is consistent with the postulated routes of excretion, with biliary excretion and loss in the faeces being the main route, and the excretion study in SGN35-008a which found that two thirds of excreted MMAE was lost in the faeces and one third in the urine. Consistent with toxicities that are dose dependent according to exposure to MMAE, administration of brentuximab vedotin to patients with impaired hepatic or renal function in Study SGN35-008b was also found to be associated with a worse adverse event profile. After review of this study, the evaluator is of the opinion that more cautious recommendations regarding the use in patients with hepatic or renal impairment are appropriate.

The 'Incidence of ATA' component of Study SGN35-005 was summarised (see Attachment 2). Inconsistent results in this study raised concerns that were the subject of a number of clinical questions to the sponsor. These concerns and the sponsor's responses to the questions posed are described above and in a clinical question (see Attachment 2: Section 12, Question 5) along with the sponsor's response. The following discussion regarding the incidence of ATA and the implications regarding the state of knowledge of immunogenicity of brentuximab vedotin is based on information provided by the sponsor in response to clinical questions and was not part of the first round CER.

Of note is that in the response to one of the clinical questions, the sponsor stated: '*Study SGN35-005 used an anti-therapeutic antibody (ATA) assay that has since been redeveloped. The former assay in use for this trial is extremely sensitive (see specifications in sponsor's response to clinical question 5 [Part b]) and thus likely returns a high rate of background positivity, regardless of randomisation therapy*.' The 'extreme sensitivity' of the assay is demonstrated by the false positive rate of 22% observed in Study SGN35-005. Narratives of infusion related reactions were provided in response to another clinical question. On review of these narratives, no discernible relationship between ATA status or titres and infusion related reactions could be identified. The evaluator is of the opinion that, given the unreliability of the assay, all of the ATA results for this study, together with any conclusions drawn from these results, should be disregarded.

[7] European Medicines Agency Assessment Report: Adcetris (brentuximab vedotin) dated July 2012.
[8] Australian Public Assessment Report for brentuximab vedotin; Proprietary Product Name: Adcetris. Sponsor: Takeda Pharmaceuticals Australia Pty Ltd. Date of AusPAR May 2014. Therapeutic Goods Administration, Canberra.

The study report of the validation study for this assay was provided in the dossier. The final study report is dated 2009, with amendments dated July 2011, December 2011 and June 2013. ATA status has been determined in other studies in the Clinical Trial Programme and the evaluator could not determine if the same assay has been used throughout the clinical development programme. Of note is that the false positive rate in Study SGN35-008b was 31%. The current PI contains the following statements:

> *'Approximately 7% of patients in the Phase II studies and 6% of patients in the Adcetris arm of the Phase III study developed persistently positive anti-therapeutic antibodies. There was a higher incidence of infusion-related reactions observed in patients with persistently positive antibodies to brentuximab vedotin relative to patients who tested transiently positive or negative.'* and *'The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin.'*

If the assay used in these earlier studies is the same assay as that used in Study SGN35-005 (the Phase III study referred to in these statements), then the evaluator is of the opinion that the results with this assay do not allow any conclusions to be drawn and these statements should be removed from the PI. The immunogenicity of brentuximab vedotin, the incidence of ATA and possible effects of ATA on safety and efficacy should be regarded as 'missing information'.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamics data was included in this submission.

Evaluator's conclusions on pharmacodynamics

No new pharmacodynamic data were included in this submission. The summary provided in Attachment 2 is based on the information provided in the previous AusPAR and currently approved PI.

Of note is that no studies investigating the postulated mechanism of action have been submitted by the sponsor. Also of note is that pharmacodynamic drug-drug interactions have been identified through other studies investigating combination regimens in the Clinical Development programme. These interactions were not described in the submission, although information regarding some of these interactions is available in the PSURs.

The evaluator noted that this information is dealt with inconsistently in the proposed PI. Concurrent use of bleomycin is listed as a contra-indication in the proposed PI. No mention is made of other possible pharmacodynamics drug-drug interactions with other chemotherapy agents and the Interactions with Other Medicine section states: '*There are no drug-drug interactions data available with other chemotherapy regimens.'* The evaluator notes the commentary in the Risk Management Plan (RMP) for this submission proposed that the PI include the information that brentuximab vedotin is indicated as monotherapy only. The clinical evaluator agrees with the RMP evaluator that it should be explicit in the PI that the safety of brentuximab vedotin in combination chemotherapy regimens has not been established.

Dosage selection for the pivotal studies

The dose of 1.8 mg/kg administered every three weeks was based on the Phase I dose escalation studies which found 1.8 mg/kg to be the maximum tolerated dose and the 3 week interval to provide the best balance between efficacy and cumulative toxicity, in particular, peripheral neuropathy. The number of cycles is limited to a maximum of 16, also due to cumulative toxicities. This dosing regimen was found to be clinically effective in the Phase II study in relapsed/refractory HL following ASCT with an acceptable toxicity profile. Use of a placebo control was considered reasonable as there is no currently registered product for the proposed indication extension.

Efficacy

Studies providing efficacy data

One study, Study SGN35-005 (AETHERA), was submitted and considered pivotal for the assessment of efficacy.

Evaluator's conclusions on efficacy

Only the summary provided here. Please see Attachment 2 *Evaluator's conclusion on efficacy* for more details.

Summary

Study SGN35-005 found that patients with CD 30+ HL who received brentuximab vedotin as consolidative therapy following ASCT had a substantially and clinically important increase in median PFS by IRF of 19 months in comparison to patients receiving placebo (median PFS of 42.9 months compared to 24.1 months). An improvement of this magnitude would be important to patients. It is concerning, however, that this did not translate into the other patient important outcomes of improved quality of life and improved overall survival.

The results of the AETHERA study also indicate that 45% of patients who received ASCT for relapsed/refractory HL would be cured by ASCT alone, that an additional 20% of patients may be cured by the use of brentuximab vedotin as consolidative therapy and that 35% of patients would progress despite brentuximab vedotin. It is evident from this, and from subgroup analyses, that there are groups within the study population who obtain varying benefits from the use of brentuximab vedotin as consolidative therapy, with one group (patients with only one risk factor for progression) appearing to fare worse.

The sponsor has estimated that 50 to 70% of patients who receive ASCT for relapsed or refractory HL would have at least one risk factor for progression post-ASCT and proposes that all of these patients receive brentuximab vedotin as consolidative therapy following ASCT. Given the varying response in the subgroups and the lack of demonstrable improvement in OS and Quality of Life (QoL) it is clear that this use of brentuximab vedotin will not benefit all of these patients. There is clearly a subgroup of patients who have been cured by ASCT and who therefore risk only harm from brentuximab vedotin therapy. Better characterisation of patients who will develop progressive disease following ASCT, and/or who will be cured by ASCT alone would enable more targeted use of brentuximab vedotin.

Safety

Studies providing safety data

The existing safety profile of brentuximab vedotin was established in the evaluation as a new chemical entity in 2012 and this is largely based on two single arm Phase II studies. Treatment-related adverse events were common in the Phase II studies resulting in treatment discontinuation in 19% or dose modifications in 46%. Safety issues of concern were Peripheral neuropathy, Neutropenia, Infection and infusion related reactions. Peripheral neuropathy was reported in 45% of patients. This required dose modification (delay or reduction) in 18% and treatment discontinuation in 12%. Peripheral neuropathies were usually mild, with 89% Grade 2 or less, and reversible with improvements occurring over a median of 16 weeks. Neutropaenia was observed in 21% of patients and was managed with dose delay and/or growth factor support. Less than half of the patients with neutropaenia had temporally associated infections and these were usually mild (Grade 1 or 2). Infections were observed in 61% of patients overall but these were usually mild and no patient discontinued treatment due to infection. One patient developed progressive multifocal leukoencephalopathy (PML) and died. Infusion related reactions occurred in 11% and were mild to moderate in severity although two cases of anaphylaxis were reported in the Phase I studies. A more detailed description of the safety aspects identified in the earlier studies can be found in the AusPAR for Brentuximab vedotin (Adcetris).[8]

Evaluable safety data

The following provided evaluable safety data:

- In the original dossier:
  - One pivotal efficacy study, Study SGN35-005
  - 5 Periodic Safety Update Reports (PSURs) covering the period from 19 August 2012 to 18 February 2015
- In the sponsor's response to clinical questions:
  - This included cumulative reviews of pulmonary toxicity and hepatotoxicity and a more recent PSUR (August 2014 to August 2015) which included a cumulative review of a new safety concern, gastrointestinal complications.
- In the Safety Related Request:
  - This included the cumulative reviews that had been provided and updated information regarding the Phase II population.
- In the CSR for Study SGN35-008b
  - This study provided information regarding the adverse event incidence in patients with renal or hepatic impairment.

Patient exposure

A total of 329 patients were enrolled and randomised to receive brentuximab vedotin (N = 165) or placebo (N = 164). Of the 329 randomised patients, 327 patients received at least 1 dose of study treatment; 2 patients randomised to receive placebo withdrew consent prior to receiving the first dose of study drug. Two patients in the placebo arm received a single dose the study drug in error and 72 patients in the placebo arm were treated with brentuximab vedotin following progression (investigator and/or IRF assessment).

Of the 327 patients, 159/327 (49%) patients completed 16 cycles of treatment, 78 patients in the brentuximab vedotin arm and 81 in the placebo arm. The median number of treatment cycles in each arm was 15 cycles (range 1 to 16). Of the 327 patients, 170 did not receive 16 cycles of treatment. The most common reason for this in the brentuximab vedotin arm was adverse events and in the placebo arm, progressive disease, as shown below in Table 1.

Table 1. Study SGN35-005 Reasons for treatment discontinuation

Reason for Treatment Discontinuation	Brentuximab vedotin group Number (%)	Placebo group Number (%)
Adverse events	54 (33%)	10 (6%)
Progressive disease	24 (15%)	69 (42%)
Patient decision	9 (5%)	4 (2%)
Total	87	83

Safety issues with the potential for major regulatory impact

Two new safety concerns were addressed in PSUR 6: gastrointestinal complications and posterior reversible encephalopathy syndrome (PRES).

Safety issues with the potential for major regulatory impact are covered in detail in Attachment 2. Topics covered include:

- Neurological toxicity including peripheral neuropathy, convulsions and PRES
- Hepatotoxicity and hepatobiliary adverse events
- Pulmonary toxicity
- Haematological toxicity including neutropaenia, febrile neutropaenia, thrombocytopaenia and anaemia
- Infection, including bacteraemia, sepsis and septic shock and opportunistic infections
- Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Cardiovascular safety, including cardiac failure/dysfunction, QT/QTc prolongation, infusion-related reactions and immunogenicity
- Infusion related reactions and immunogenicity
- Other safety issues, including pancreatitis, gastrointestinal toxicity, progressive multifocal leukoencephalopathy (PML), hyperglycaemia, tumour lysis syndrome and thymic depletion.
- Safety in special populations, including renal or hepatic impairment, elderly, paediatrics, breastfeeding and drug-drug interactions.

Post-marketing data

Six PSURs were available covering the period from 19 August 2012 to 18 August 2015.

In PSUR 6, the cumulative estimated patient-exposure to brentuximab vedotin is 22,240 patients, including 2415 in company sponsored clinical trials. The highest usage is reported in the USA and Europe.

A full analysis of post-marketing data is available in Attachment 2.

Evaluator's conclusions on safety

Treatment with brentuximab vedotin was described as well-tolerated. Despite this, only 47% of patients in the pivotal Phase III study, Study SGN35-005 were able to complete the proposed 16 cycles of treatment. Adverse events (AE) have been shown to occur commonly with brentuximab vedotin with at least one treatment-related AE of any grade reported in 88% of patients in the brentuximab vedotin arm of Study SGN35-005. Most of these AES were minor and the most common, peripheral neuropathy and neutropaenia, were reversible and could usually be managed by dose delay. However, more serious adverse events (SAE) (Grade 3 or higher) were reported in 44% of patients and 32% discontinued treatment with brentuximab vedotin due to AEs. A considerable proportion of patients required dose delays (54%) or dose reduction (32%) to manage adverse events.

The evaluator notes that the quality of life measurements (See Attachment 2: Section 7, 'Results for the other efficacy outcomes, Quality of life assessments' for further details) appear inconsistent with the rate of occurrence of AEs reported in the study. According to the instrument used, there was little change in the quality of life measure from baseline to the end of the follow-up period for those patients who did not develop progressive disease. Despite this, AEs in 32% of the patients in the brentuximab arm were significant or distressing enough for these patients to discontinue treatment.

The safety assessment provided by the sponsor referred only to Study SGN35-005. As a consequence, serious albeit rare, risks associated with brentuximab vedotin treatment were not given sufficient consideration in the benefit-risk evaluation provided by the sponsor. Safety issues of concern identified in the whole clinical trials programme were common AEs including peripheral neuropathy, neutropaenia, infection, hyperglycaemia and infusion related reactions together with the rare risks of serious skin reactions and PML. Post-marketing reports and cumulative reviews of the clinical studies safety data have identified a number of other real or potential risks that have been associated with fatal outcomes, including acute pancreatitis, febrile neutropaenia, severe sepsis/septic shock, opportunistic infection, hepatotoxicity with fulminant hepatic failure, pulmonary toxicity with monotherapy resulting in pneumonitis and ARDS, serious skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), anaphylaxis and gastrointestinal complications.

Common AEs

- Treatment emergent peripheral neuropathy (PN) was reported in 67% of patients in the brentuximab vedotin arm of Study SGN35-005, 56% of patients in the Phase II Population and is the most common spontaneously reported AE from post-marketing sources. In the patients in the brentuximab arm of the Phase III study, the PN was usually mild (Grade 3 severity in 13% and no Grade 4 severity), reversible, described as having little effect on quality of life and was managed by dose delay or reduction. Despite this, one third of the patients who developed PN discontinued treatment with brentuximab vedotin due to this AE.
- Neutropaenia was reported in 35% of patients in the brentuximab vedotin arm of Study SGN35-005, 21% of patients in the Phase II population and is the cause of a number of spontaneous reports from post-marketing sources. In the clinical studies, neutropaenia appeared to be well managed by dose delay and growth factor support.

In the Phase III study, Grade 4 neutropaenia was reported in a small number of patients and there was one report of febrile neutropaenia. In the Phase II Population, there was one report of febrile neutropaenia and septic shock with a fatal outcome. Febrile neutropaenia with fatal outcomes has also been reported from post-marketing sources. Other manifestations of haematological toxicity, including anaemia and thrombocytopaenia, have been reported during brentuximab vedotin therapy.

- Infections were common in the clinical studies, although these were most commonly mild with upper respiratory tract infection in 26% of brentuximab vedotin patients in the Phase III study. Serious infections were uncommon and reported for 9% in the brentuximab vedotin arm of the Phase III study and 10% of the Phase II population. Serious infections in the Phase III study included pneumonia and opportunistic infections such as reactivation of herpes zoster, herpes simplex and one case of *Pneumocystis jiroveccii* pneumonia. Many of these infections were also reported for the placebo arm, although at a lower incident rate. There were 2 deaths from opportunistic infection in the Phase II population and a number of opportunistic infections with fatal outcome have been reported by post-marketing sources, including aspergillosis, cytomegalovirus and *pseudomonas* infection.
- Infusion-Related Reactions (IRR) was reported in 15% of patients in the brentuximab vedotin arm of Study SGN35-005, 11% of patients in the Phase II population and was frequently reported by post-marketing sources. The adverse events most commonly associated with infusion-related reactions were mild to moderate (Grade 1 or Grade 2) and included headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, and cough. No cases of anaphylaxis have been reported in the Phase II or III populations, although 2 cases were reported in the Phase I population. There have been 4 reports of fatal outcome in association with IRR from post-marketing sources. Measurement of ATA in patients exposed to brentuximab vedotin seem to indicate that patients who become 'persistently positive' are more likely to have IRRs and that these reactions may be more severe. The reliability of the assay on which this conclusion is based is questioned and these conclusions may not be valid. IRRs in the clinical study population were usually successfully managed by infusion interruption, treatment of the reaction, followed by recommencement of the infusion at a lower rate. Subsequent doses were administered with or without prophylaxis. The EU Summary of Product Characteristics (SmPC) recommends the use of prophylaxis with subsequent doses if a patient experiences an IRR and discontinuation if anaphylaxis occurs.
- Hyperglycaemia has been reported in 3% of the Phase II study population and 7% of the Phase II population. Predisposing factors are thought to be obesity or pre-existing hyperglycaemia. It was usually managed by insulin or oral hypoglycaemics.

Uncommon and unpredictable adverse events

A number of rare, life-threatening adverse events have been observed in association with brentuximab vedotin. Of these, hepatotoxicity and gastrointestinal complications were predictable from the non-clinical studies. However, pulmonary toxicity with monotherapy, serious skin reactions, acute pancreatitis and gastrointestinal complications were not. A direct causal relationship has not been established for each of these risks.

- Hepatotoxicity was reported in 7% of patients in the brentuximab vedotin arm of Study SGN35-005. The incidence in the clinical studies programme has been estimated at 1.4%. The majority of events in the studies were asymptomatic with mild to moderate transient elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) that occurred after 1 to 2 treatment cycles and were reversible. A number of cases of severe or fulminant hepatitis have been reported from the clinical studies and from post-marketing sources, including one case from the Phase III study. Some of these cases have had fatal outcome. Hepatotoxicity was

identified as an Important Potential Risk in 2013. Following a cumulative review of hepatotoxicity performed in 2015, the sponsor has suggested strengthening the warning in the PI.

- Pulmonary toxicity was reported in 5% of patients in the brentuximab vedotin arm of the Phase III study and for 3% of the overall clinical studies population. It usually manifested as a mild disorder with cough, dyspnoea and lung infiltrates. More severe pulmonary toxicity with acute respiratory distress syndrome (ARDS) has also been described and has been associated with fatal outcome, including 2 deaths attributed to ARDS in the Phase III study. Pulmonary toxicity with monotherapy was listed as an Important Potential Risk in the SmPC in 2014. Following a cumulative review of pulmonary toxicity with monotherapy performed in 2015, the sponsor has suggested strengthening the warning in the PI.
- Acute pancreatitis has been reported in a small number of patients from the clinical studies population (incidence < 1%), including one patient from the brentuximab vedotin arm of the Phase III study. The disorder was commonly severe and has been associated with fatal outcome. Acute pancreatitis was listed as an Important Potential Risk in the SmPC in 2013.
- Stevens-Johnson syndrome (SJS) in association with brentuximab vedotin therapy was reported early in the clinical trials programme, with an estimated incidence of 1%. Two cases of toxic epidermal necrolysis (TEN), each with a fatal outcome, have been reported: one from the clinical trials programme and one from post-marketing sources. TEN, together with SJS, was therefore identified as a new and important risk with brentuximab vedotin. This information was added to the SmPC and also included in the boxed warning regarding risks with possible fatal outcomes in the Canadian PI.
- PML has been has been reported in no patients who have received brentuximab vedotin after receiving multiple prior chemotherapy regimens, 7 of whom have died and the outcome is unknown for one. The reporting rate is estimated at less than 0.05% and a causal relationship has not been established.
- Tumour lysis syndrome has been reported in a small number of patients receiving brentuximab vedotin and has been associated with fatal outcome.
- Other safety signals, such as cardiac dysfunction, PRES and thymus depletion are being closely monitored.

A number of other questions regarding the safety profile of brentuximab vedotin have yet to be answered. These include use in special populations (paediatric, elderly, renal or hepatic impairment) and immunogenicity, including the effects of ATA on efficacy and safety. Determining the meaning and significance of anti-brentuximab vedotin antibodies will require development of a more precise assay. Wider use and reports from post-marketing sources may identify other safety concerns or help refine existing ones (for example, cardiac dysfunction). Possible delayed adverse effects of brentuximab vedotin (in particular, secondary malignancies) may yet be identified through prolonged follow-up of the clinical studies populations.

First round benefit-risk assessment

Please see *First round benefit-risk assessment* in Attachment 2 and *Second round benefit risk assessment* below.

First round recommendation regarding authorisation

The evaluator is unable to make a recommendation at this time.

Clinical questions

For details of the evaluator's clinical questions, please see Attachment 2.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefit of brentuximab vedotin in the proposed usage is a substantial increase in PFS when used following ASCT for adult patients with relapsed or refractory CD 30+ HL at increased risk of progression following ASCT. This increase was clinically relevant and statistically significant. However, the demonstrated increase in PFS did not translate into an improved quality of life so it cannot be said that patients were both remaining disease free for longer and 'living better'. The increase in PFS also did not translate into an increase in OS, although OS results were immature at the time of the analysis.

The patient population in the pivotal study presented was heterogeneous with regard to risk of progression following ASCT and subgroup analyses showed that all groups did not receive equal benefits from brentuximab vedotin. Those groups at highest risk of progression according to historical data (refractory disease after frontline therapy, > 2 treatment lines prior to ASCT, B symptoms at the time of relapse prior to ASCT, partial response to salvage therapy and the presence of 3 or more risk factors) appeared more likely to benefit. The group historically at low risk of progression (relapse after 12 months, ≤ 2 prior treatment lines, absence of B symptoms after frontline therapy, CR following salvage therapy) appeared to gain little benefit in terms of PFS with brentuximab vedotin. One subgroup at low risk of progression, as shown by the presence of only one risk factor, appeared to fare worse with brentuximab vedotin.

Better characterisation of patients at greatest risk of progression and/or at least risk may enable better targeting of this therapy. Apart from identifying the patients with one risk factor as a group least likely to benefit and the group with 3 or more risk factors as more likely to progress, the additional subgroup analyses requested by the evaluator were unhelpful with regards to this desired better characterisation. It is possible that an absolute determination of the patients group that is most likely to benefit and least likely to be harmed with brentuximab vedotin in the proposed usage is not possible with currently available information.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of brentuximab vedotin in the proposed usage are those of morbidity and mortality due to adverse events or complications of brentuximab vedotin therapy. There is also the risk that, despite the increase in progression free survival, quality of life may not be improved and the patients may receive little benefit from the extra months of life.

Morbidity and mortality due to complications of therapy

Complications of brentuximab vedotin treatment may be divided into predictable and idiosyncratic.

Predictable complications

Adverse events are common with brentuximab vedotin therapy (88% of patients in the brentuximab arm of Study SGN35-005 experienced treatment-emergent adverse events (TEAE). Their occurrence is believed to be due to 'off-target' effects of free MMAE and to the effects on non-malignant CD30+ lymphocytes. The following adverse events have been observed with brentuximab vedotin therapy.

- Neutropaenia is reported in over a third of patients during brentuximab vedotin therapy. It may be prolonged (≥ 1 week) or severe (Grade 3 or Grade 4). It can usually be managed by monitoring, dose delay and growth factor support. However, febrile neutropaenia has been reported as an SAE in 8% of patients receiving brentuximab vedotin and deaths from this have been described.
- Peripheral neuropathy is a cumulative dose dependent toxicity that has been described in almost half of the patients receiving brentuximab vedotin, and may be severe. It may be managed by dose reduction or discontinuation and is usually reversible, but this may take a prolonged time (median 16 weeks). Peripheral neuropathy was the cause of treatment discontinuation in 21% of patients in the brentuximab vedotin arm of Study SGN35-005.
- Serious infections, such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes), and opportunistic infections such as oral candidiasis, *Pneumocystis jirovecii* pneumonia and herpes zoster, have been reported in patients treated with brentuximab vedotin. These have resulted in fatal outcomes.
- Tumour lysis syndrome has been reported infrequently but has been associated with fatal outcome.
- Infusion related reactions occur commonly during brentuximab vedotin therapy and have included fatal anaphylaxis. The relationship of these reactions to the development of anti-therapeutic antibodies to brentuximab vedotin cannot be determined due to issues related to the ATA assay used.

Idiosyncratic reactions

A number of rare, unpredictable adverse events have been reported with brentuximab vedotin therapy. A clear causal relationship has not been identified for all of the complications listed below but they have been recognised as important risks ('identified' or 'potential'). Cumulative reviews performed in 2015 have strengthened the concerns related to hepatotoxicity and pulmonary toxicity. Gastrointestinal complications were recognised as an important potential risk, also in 2015. The complications listed here have all been associated with fatal outcome:

- Acute pancreatitis
- Hepatotoxicity. This may occur in 1% of patients receiving brentuximab vedotin and is usually a mild, reversible hepatocellular injury. However, fulminant hepatitis has also been described in patients receiving brentuximab vedotin.
- SJS and toxic epidermal necrolysis.
- PML
- Infusion related reactions, including life-threatening anaphylaxis

- Pulmonary toxicity with cough, dyspnoea and lung infiltrates. ARDS has also been reported.
- Gastrointestinal complications
- Secondary malignancies

The risk of death from each of these adverse events or reactions is small. The cumulative risk of death from these possible complications of brentuximab vedotin treatment can be approximated from data provided in the most recent PSUR (PSUR 6) and data from the cumulative reviews provided by the sponsor in response to clinical questions.

Table 2. Approximate risk of death due to adverse events with fatal outcome reported with use of brentuximab vedotin

Complication	Fatality rate (%)	Source, number of fatal events/population
Peripheral neuropathy	0.006	Post marketing sources 1/16238
Tumour lysis syndrome	0.012	Post marketing sources 2/16238
Febrile neutropaenia	0.07	Clinical Study Programme 2/2962
Anaemia, thrombocytopenia	0.03	Post marketing sources 5/16238
Infection Including Bacteraemia/Sepsis/Septic Shock	0.6	Clinical Study Programme 18/2962
Opportunistic infection	0.07	Clinical Study Programme 2/2962
Infusion related reactions	0.07	Clinical Study Programme 2/2962
PML	0.04	All sources 9/22240
SJS/TEN	0.03	Clinical Study Programme 1/2962
Acute pancreatitis	0.04	Post marketing sources 7/16238
Hepatotoxicity*	0.11	'Solicited sources' 6/5475
Pulmonary toxicity (monotherapy)*	0.53	Company sponsored studies (monotherapy) 3/562
Gastrointestinal complications	0.11	Clinical trials 6/5748
Secondary malignancy	?	?
Total	1.68	
Analysis assumes 1) all deaths were due to the reported AE and that these, in turn, were due to brentuximab vedotin; 2) individual cases were not reported for more than one category; 3) no data regarding the incidence and fatality rate of secondary malignancies was available		

Other risks due to complications of brentuximab vedotin therapy relate to missing information. Safety in the elderly, children, and patients with cardiac impairment has not

been established. The safety in the setting of possible risk factors for complications such as pre-existing hepatic impairment and hepatotoxicity and pre-existing lymphomatous involvement of the gastro-intestinal tract and bowel perforation has not been established. The relationship of anti-therapeutic antibodies to safety and efficacy has not been determined. Given that brentuximab vedotin has only been available commercially for 4 years, there may be other rare complications and delayed complications that have yet to be identified.

Quality of life

This was assessed in Study SGN35-005. According to the instrument used (EQ-5D), quality of life reported by study participants for the 24 month duration of the study was no better for the patients who received brentuximab vedotin compared to placebo. The ability of this instrument to detect changes in quality of life must be questioned, though, as there was minimal change in quality of life across the study for all patients who did not develop progressive disease. This is surprising as the baseline measure was taken within 30-45 days of autologous stem cell transplant and an improvement in quality of life may have been expected as patients recovered from this. Other markers of the quality of life impact of brentuximab vedotin therapy in this study may be the number of patients who discontinued treatment due to adverse events and any changes in the Eastern Cooperative Oncology Group (ECOG) status of patients during the study. Of the patients receiving brentuximab vedotin, 32% discontinued treatment due to AEs, compared to 6% in the placebo arm. Peripheral neuropathy (motor and/or sensory) was the most common reason for patients in the brentuximab vedotin arm to cease treatment (21%). The severity of peripheral neuropathy is variable but is usually reversible. This may, however, take some months and could be expected to impact on the patient's quality of life during this time. Each patient's ECOG status was assessed regularly throughout the study. In comparison to baseline, ECOG status remained unchanged for many patients. However, it was noted to worsen in 59 patients (36%) in the brentuximab vedotin arm compared to 39 patients (25%) in the placebo arm and to improve in 36 patients (22%) in the brentuximab vedotin arm compared to 43 patients (27%) in the placebo arm.

Second round assessment of benefit-risk balance

The benefit-risk balance of brentuximab vedotin is unfavourable for the proposed usage, but could become favourable if the changes recommended in this section (Second round assessment of benefit-risk balance) and changes recommended regarding the draft PI [not included in this document] are adopted.

The evaluator recognises the importance of the improved progression free survival demonstrated in the pivotal study but is concerned by the lack of improvement in quality of life and the lack of benefit in overall survival. It is not clear to the evaluator that the use of brentuximab vedotin as adjuvant therapy offers a meaningful improvement over its use as rescue therapy. The evaluator is also concerned that, with the proposed usage, there will inevitably be patients who would otherwise have been cured by ASCT who will be exposed to the potentially fatal complications associated with brentuximab vedotin. Individually these potentially fatal adverse effects are rare. However, together they add up to a substantial risk to the patients.

The evaluator is also of the opinion that the potential risks associated with brentuximab vedotin have not, as yet, been fully characterised. Brentuximab vedotin has been available in the wider non-trial population for only a few years – it was first approved for marketing in the US in 2011. During this time, the concerns regarding toxicity of brentuximab vedotin have increased considerably due to the progressive recognition of many of the life-threatening complications associated with treatment that have been detailed above. An

example of this is the identification of the association with potentially fatal gastrointestinal complications that has occurred in just the last few months.

Under the currently approved indications, patients receiving brentuximab vedotin have poor prognosis and no other less toxic therapeutic options. At the time of this approval in December 2013, the Delegate noted:

> '*The most significant common toxicity was peripheral neuropathy, which may detract from quality of life and may require discontinuation from treatment. There were rarer, more serious AEs, for example anaphylaxis; Stevens-Johnson syndrome (SJS)/TEN; possibly PML (the signal for this latter AE was difficult to distinguish from baseline).'*

As detailed above, the risk profile for brentuximab vedotin has worsened since the approval as a new chemical entity (NCE). In those patients who are treated under the current indications, and for whom the prognosis is very poor and alternative therapies of little benefit, the risks associated with brentuximab vedotin would remain acceptable. However, with the proposed usage, patients who would be cured by ASCT alone will be exposed to brentuximab vedotin. The risks to these patients are considerable and the benefit nil. Unfortunately, with the information provided by the sponsor, those patients who would not benefit from this adjuvant therapy cannot be identified.

For brentuximab vedotin to be considered for adjuvant therapy, several measures are required to ensure that appropriately informed prescribing (within the limits of current knowledge) occurs, that patients are fully cognisant of the potential risks and benefits and that timely emergency care is provided to patients developing potentially life-threatening complications. This will require:

- Substantial rewording of the proposed indication to:

  'Treatment of adult patients with CD30+ HL at high risk of relapse or progression following ASCT, as shown by the presence of two or more risk factors (see Clinical Trials).

  This indication was approved based on promising progression free survival in a placebo controlled trial. The data did not demonstrate an increased survival or improved quality of life with Adcetris'.

- Explicit recognition of the risks associated with the use of brentuximab vedotin is required in both the PI and CMI is essential to ensure most appropriate prescribing and informed consent. This should include a boxed warning at the beginning of the PI and CMI as shown:

Figure 4. Boxed warning for the PI

Serious Warnings and Precautions

Clinically significant and/or life threatening and/or fatal adverse events have been reported with the use of Adcetris.

These include: JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), serious and opportunistic infections, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, hepatotoxicity, pulmonary toxicity, acute pancreatitis and gastrointestinal complications

(see Precautions*)*

Figure 5. Boxed warning for the CMI

Other changes to the proposed PI and CMI as recommended by the evaluator [are beyond the scope of this document].

To assist the prescriber in providing the necessary information to the patient, the PI should include a 'Patient Counselling Section'.

- A registry of the use of brentuximab vedotin as both rescue and adjuvant use in the Australian population. This will provide 'real-world data' of safety and efficacy and may assist in better characterisation of identified safety concerns and in the recognition of any new safety concerns. Reliance on voluntary reporting of adverse events is inadequate for this. The financial cost of this registry should be borne by the sponsor.
- A patient safety card with information on one side that advises the patient of when to seek urgent medical attention and information on the other side to advise medical practitioners providing emergency care of the complications unique to this medication. [Further discussion of this is beyond the scope of this document].
- A healthcare professional information brochure to provide easily accessible information for all healthcare professionals involved in the care of the patients receiving brentuximab vedotin should be available. This should supplement but not replace the PI and should be provided for display in locations in which brentuximab vedotin will be administered.

In addition, further studies to assist in identification of the group that progress early and receive little benefit from brentuximab vedotin and the group that respond well to ASCT alone would enable those patients most likely to benefit receive the therapy and those least likely to benefit, or who may be harmed by the therapy, do not receive it.

Second round recommendation regarding authorisation

The second round recommendation regarding authorisations is unfavourable but could become favourable if the changes recommended in above and changes recommended to the product documentation are adopted. The evaluator is also of the opinion that it may be helpful to obtain advice from independent Australian specialists experienced in the care of patients with relapsed/refractory HL to assist in the decision making process.

The evaluator considers that the decision regarding approval of brentuximab vedotin for the proposed extension of indication is complex. Of note is that submissions for the same extension of indication and using the same dataset were made to the FDA on 18 February 2015 and to the EMA on 11 March 2015. From publically available information, these submissions have had different outcomes.

- The extension of indication was approved in August 2015 by the FDA with the wording: *'Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation'.* In the approved labelling, the reader is referred to the Clinical Trials section where '*High risk of post-auto-HSCT relapse or progression was defined according to status following frontline therapy: refractory, relapse within 12 months, or relapse ≥ 12 months with extra-nodal disease. Patients were required to have obtained a CR, PR, or stable disease (SD) to most recent pre-auto-HSCT salvage therapy*'.

- At the time of this evaluation, no decision had been reached by the EMA and no final recommendation has been made by the Committee for Medicinal Products for Human Use (CHMP). According to publically available documents, the sponsor's application was discussed at both the June 2015 and October 2015 CHMP meetings and is to be discussed again at the April 2016 meeting. The June 2015 meeting minutes note that the '*The Committee agreed to seek clarification on the benefit/risk in the proposed extension of indication with specific focus on the target population'.* The October meeting minutes note that a discussion of issues identified in the application focussed on '*the clinical efficacy and the outcome seen for progression free survival versus overall survival. Furthermore the safety profile was discussed in relation to the drop-out rate of the clinical trial.'* The publically available agenda for the April 2016 CHMP meeting has the proposed extension of indication for discussion again, with this including an *'Oral explanation, report by [information redacted] from SAG Oncology meeting held on 14 April 2016'* and notes that an additional request for supplementary information was made in January 2016.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan, EU-RMP Version 5.2 (dated 23 February 2015, Data Lock Point 18 August 2014) and Australian-specific annex (ASA) Version 5.0 (dated July 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 3, as follows.

Table 3. Summary of ongoing safety concerns identified by sponsor

Safety concern	Details
Important identified risks	Progressive multifocal leukoencephalopathy Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin Peripheral neuropathy (sensory and motor) Neutropaenia Febrile neutropaenia Thrombocytopaenia Anaemia Infection including bacteraemia/sepsis/septic shock Opportunistic infection Infusion-related reaction Hyperglycaemia Stevens-Johnson syndrome/Toxic epidermal necrolysis Tumour lysis syndrome

Safety concern	Details
	Anti-therapeutic antibodies
Important potential risks	Pancreatitis acute Hepatotoxicity Pulmonary toxicity Reproductive toxicity Thymus depletion (paediatric) Infection with drugs modifying CYP3A4 activity
Missing information	Safety in paediatrics Safety in the elderly Safety in patients with hepatic, cardiac or renal impairment Long term safety

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities. These activities are summarised in Table 4, below.

Table 4. Summary of proposed pharmacovigilance activities

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Submission Date of Interim / Final Report (Planned / Actual)
SG035-0004: Ph 2 study of SGN-35 in treatment of patients with r/r sALCL (Category 2)	Single-agent efficacy, safety, PK	Peripheral neuropathy (sensory & motor)	CSR finalized: Dec 2011	Jan 2012 (actual)
			LTFU ongoing	Annual reports: Until 2016 or until OS data are sufficiently mature (≥ 50% OS events observed), whichever occurs earlier
SGN35-005 (AETHERA): Randomized, double-blind, placebo-controlled, ph 3 study of brentuximab vedotin and best supportive care (BSC) versus placebo (PBO) and BSC in treatment of patients at high risk of residual HL following autologous stem cell transplant (ASCT) (Category 3)	Efficacy (PFS, OS), safety	Peripheral neuropathy (sensory & motor); antitherapeutic antibodies (ATAs); IRRs, pulmonary toxicity (devoid of concomitant bleomycin)	Primary endpoint completed; LTFU ongoing	CSR (primary endpoint): Dec 2014 (actual; see Annex 9)
SGN35-014: Randomized, double-blind, placebo-controlled, ph 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in frontline treatment of patients with CD30-positive mature T-cell lymphomas (MTCLs) (Category 3)	Multi-agent efficacy (PFS, OS, CR); safety	Peripheral neuropathy (sensory & motor); IRRs; ATAs	Ongoing	CSR (primary endpoint): Sep 2018
C25001: Randomized, open-label, ph 3 trial of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in patients with CD30-positive cutaneous T-cell lymphoma (Category 3)	Comparison with physician's choice; efficacy (ORR, PFS, CR, OS); safety	Peripheral neuropathy (sensory & motor); IRRs (baseline & safety); ATAs (baseline & safety)	Ongoing	CSR (Registration): Jul 2016 LPEOT: Dec 2015 CSR addendum (LTFU): Nov 2018
C25002: Ph 1/2 PIP study of brentuximab vedotin in pediatric patients with r/r sALCL or HL (Category 3)	Safety; PK; pediatric maximum tolerated dose (MTD) and/or RP2D Immunogenicity, antitumor activity	Safety in pediatrics; thymus depletion (pediatric); ATAs	Ongoing	CSR (primary analysis): Dec 2016 CSR addendum (LTFU): Aug 2017
C25004: Ph 1, open–label, PIP study of OEPA followed by SGN-35 and COPDAC in pediatric patients with high-risk, newly diagnosed HL (Category 3)	Safety; determination of MTD or highest HPD in combination Evaluation of PK, immunogenicity, activity of combination therapy, and mobilization of peripheral blood stem cells for ASCT	Safety in pediatrics; thymus depletion (pediatric)	Planned	LPO: On/before Dec 2018
C25005: Ph 1 study to estimate MMAE metabolites in human plasma and urine in patients with r/r classical HL or r/r sALCL receiving brentuximab vedotin (Category 3)	Estimation of MMAE and metabolites; concentration of antibody-drug conjugate (ADC) and total antibody (TAb) in serum; ATAs; safety	ATAs	Ongoing	Primary endpoint CSR: Oct 2015 Final CSR (safety): Feb 2016
C25006: Ph 4, open-label, single-arm study of brentuximab vedotin in patients with r/r sALCL (Category 2)	Single-agent efficacy (ORR, duration of tumor control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT; OS), safety and tolerability, PK, immunogenicity	ATAs	Ongoing	Primary CSR: Q1 2016 LTFU CSR: Q2 2020
C25007: Ph 4, open-label, single-arm study of brentuximab vedotin in patients with r/r HL who are not suitable for SCT or multiagent chemotherapy (Category 2)	Single-agent efficacy (ORR, duration of tumor control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT, OS), safety and tolerability, PK, immunogenicity	Peripheral neuropathy (sensory & motor); IRRs; ATAs	Ongoing	Primary CSR: Q2 2016 LTFU CSR: Q3 2020
MA25101 (PASS): Observational cohort study of the safety of brentuximab vedotin in the treatment of r/r CD30+ HL and r/r sALCL (Category 2)	Safety; identification of potential risk factors for peripheral neuropathy	Peripheral neuropathy (sensory & motor); neutropenia; infection including bacteremia/sepsis/ septic shock; opportunistic infection; IRRs; hyperglycemia; febrile neutropenia; pulmonary toxicity (devoid of concomitant bleomycin); safety in elderly; longer-term safety	Ongoing	Interim CSR: Apr 2016 Final CSR: Dec 2018

Information current as of 18 August 2014; all dates must be considered preliminary/estimated.

Abbreviations: A+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; ADME = absorption, distribution, metabolism, excretion; ASCT = autologous stem cell transplant; ATA = antitherapeutic antibody; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; COPDAC = prednisone, dacarbazine, cyclophosphamide, and vincristine; CR = complete response; CSR = clinical study report; DBL = database lock [date]; HL = Hodgkin lymphoma; HPD =highest planned dose; IRR = infusion-related reaction; LPEOT = last patient end of treatment; LPO = last patient out; LTFU = long-term follow-up; MMAE = monomethyl auristatin E; MTD = maximum tolerated dose; OEPA = prednisone, doxorubicin, vincristine, and etoposide; ORR = overall response rate; OS = overall survival; PASS = postauthorization safety study; PBO = placebo; Ph = phase; PFS = progression-free survival; PIP =pediatric investigational plan; PK = pharmacokinetic(s); r/r = relapsed [or] refractory; RP2D =recommended phase 2 dose; sALCL = anaplastic large cell lymphoma (systemic); SCT = stem cell transplant.

Risk minimisation activities

At the first round stage, the sponsor is not planning any additional risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Table 5 (below) summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the clinical evaluators through TGA requests and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	The sponsor acknowledges that further change to the RMP may be requested and commits to responding to these as they occur.	This is considered acceptable in the context of this application for RMP purposes.
2-3. Administrative questions and recommendations.	An updated ASA was included as requested	This is considered acceptable in the context of this application for RMP purposes.
4. The sponsor should provide an update on Studies NCT01780662, C25003, SGN35-011, SGN35-014, and X25001 with regard to interactions with other anticancer agents.	An update on the requested studies was provided.	The sponsor's response has been noted.
5. The sponsor should provide a summary of the post-market experience with overdose.	*Background*: Overdose is the administration of a quantity of a medicinal product given per administration or day that is above the maximal recommended dose according to the authorised PI. Overdose can be accidental, prescribed or intentional, with clear labelling guidelines a key in minimising medication errors. Depending on the therapeutic index of the drug and the dose given to the patient, an adverse drug reaction may or may not be the outcome of an overdose. A post-market analysis of the Global Safety Database (GSDB) for brentuximab vedotin was performed to provide a summary of the post-marketing experience with overdose and to determine if there is an association of overdose and adverse events. *Methodology*: The Marketing Authorisation Holder (MAH) performed a cumulative review of the GSDB with a data lock point of 15 January 2016 for all cases from post-marketing sources (literature, spontaneous, post-marketing surveys and regulatory authorities' reports) that met an Overdose specialized search query criteria, which encompasses the following 4 preferred terms: High	The sponsor's response has been noted.

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	Level Term (HLT): Overdose Not Otherwise Classified (NEC); Preferred Term (PT): Overdose; PT: Intentional Overdose; PT: Prescribed Overdose; PT: accidental overdose. As of 18 November 2015 (last exposure data cut prior to risk assessment), it was estimated that a total of 24041 patients had received at least 1 dose of brentuximab vedotin. Of these patients 17,938 had been treated in the post marketing setting. *Results*: As of 15 January 2016 (the data cut-off date for this analysis), 63 cases had met the Overdose SSQ criteria, including: 62 non-serious case reports (PT: overdose) received from post marketing surveys; no AEs were reported in association with these reports. 1 non-serious case report (PT: prescribed overdose) was received from a spontaneous literature source. The patient was receiving Adcetris at an unknown dose for T-cell lymphoma. During treatment, the patient experienced a 13 kg weight loss reported as non-serious. It was reported that the Adcetris dose was not adjusted according to the patient's reduced weight. According to the Adcetris SmPC Section 4.2, Posology and method of administration, the recommended dose for Adcetris is 1.8 mg/kg administered as an IV infusion over 30 minutes every 3 weeks. The patient, therefore, was thought to have received a higher dose of Adcetris in Cycle 6. A reduced dose of Adcetris was administered in Cycle 7. The patient presented with a sensory neuropathy in Cycle 6 and developed a Grade 4 motor neuropathy in Cycle 7. The events of sensory and motor neuropathy were attributed to study drug. Peripheral neuropathy, including sensory and motor neuropathy, is a well- known risk of Adcetris and is described in the labelling reference documents as very common adverse reaction. Conclusion: The MAH conducted an analysis of the GSDB and provided the summary of post-marketing experience with overdose. The vast majority of cases did not report an adverse event in association with an overdose. The MAH will continue to monitor for and evaluate cases of overdose events and associations of adverse drug events reported with brentuximab vedotin use.	
6. In the 'Indications' section, the Delegate may wish to consider including a statement that brentuximab is indicated as monotherapy only (or a statement to that effect).	The sponsor maintains that the indication as proposed remains appropriate. This item will be addressed in the pre-ACPM response if required.	This is considered acceptable in the context of this application for RMP purposes subject to approval by

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
		the Delegate.
7. In the 'Interaction with other Medicines' section, the PI should clearly state that brentuximab should not be used concomitantly with other anticancer agents (or a statement to that effect).	The sponsor disagrees with the evaluator's recommendation. Evidence exists suggesting that concomitant bleomycin, as currently contraindicated, should be avoided due to an increased rate of pulmonary toxicity. However, completed Phase I studies and ongoing Phase III studies of brentuximab vedotin in combination with other multi-agent chemotherapy regimens suggests a manageable safety profile in these combinations as follows: Completed Phase I Study SGN35-009; and ongoing but fully enrolled Phase III Study C25003: Evidence of pulmonary toxicity with concomitant bleomycin; evidence of a manageable safety profile combination with AVD (doxorubicin, vinblastine, and dacarbazine). The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and brentuximab vedotin was explored in patients with advanced-stage, newly diagnosed HL in completed Study SGN35-009. In this study, pulmonary toxicity was observed with the concomitant use of bleomycin, leading to its contraindication in combination with brentuximab vedotin. The study was amended to continue with the AVD combination and brentuximab vedotin, and further instances of pulmonary toxicity were not observed. During the trial, 51 patients received ≥ 1 dose of brentuximab vedotin. The maximum tolerated dose of brentuximab vedotin when combined with ABVD or AVD was not exceeded at 1.2 mg/kg. After completion of frontline therapy, a total of 21 (95%) of the 22 patients who received brentuximab vedotin + ABVD achieved CR, as did 24 (96%) of the 25 patients who received brentuximab vedotin + AVD. TEAEs were generally ≤ Grade 2. SAEs occurred in 41% of all patients (14 (56%) in the brentuximab vedotin + ABVD group and 7 (27%) in the brentuximab vedotin + AVD group). SAEs reported in ≥ 10% of patients overall included febrile neutropaenia (4 (16%) in the brentuximab vedotin + ABVD group versus 2 (8%) in the brentuximab vedotin + AVD group). The increased incidence of pulmonary toxicity noted in the brentuximab vedotin + ABVD group compared with the brentuximab vedotin +AVD was attributed to the brentuximab vedotin + bleomycin combination and resulted in the current labelled contraindication for this combination. The combination of brentuximab vedotin + AVD administered in this study was considered generally well tolerated. This study supported the initiation of the company-	This is considered acceptable in the context of this application for RMP purposes subject to approval by the Delegate.

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	sponsored Phase III Study C25003 of brentuximab vedotin + doxorubicin, vinblastine and dacarbazine (A + AVD) versus doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as a frontline treatment for advanced classical HL (ECHELON-1 study). Data from Study SGN-009 are referenced in the 4 articles footnoted below.[9][10][11][12] The combination of AVD and brentuximab vedotin is currently being explored versus ABVD alone in randomised Phase III Study C25003; the primary endpoint is modified PFS, and study completion is anticipated in 2018. This ongoing Study C25003 is being monitored by an Independent Data Monitoring Committee (IDMC). In March 2015, an ad-hoc IDMC meeting was convened to review safety data from the first 827 patients enrolled in Study C25003. Based on this review, the IDMC recommended that the trial should continue unmodified. The IDMC also recommended that colony-stimulating factors (CSF) be given prophylactically to all new patients randomised to the brentuximab vedotin +AVD arm beginning with treatment Cycle 1. The IDMC noted that the overall rate of febrile neutropaenia reported in the BV + AVD arm was 18%, which approximates the 20% risk level for prophylactic growth factor use that is recommended by the American Society of Clinical Oncology (ASCO) and the European Organization for Research and Treatment of Cancer (EORTC). Following the IDMC's recommendations, MAH issued a Dear Investigator Letter to the study principal investigators on 10 April 2015 to recommend that CSF be given prophylactically to all new patients randomized to the BV + AVD arm beginning with treatment Cycle 1. Data from ongoing Study C25003 (ECHELON-1) are referenced in the following 4 articles footnoted below.[13][14][15][16]	

[9] Connors J, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed advanced stage Hodgkin lymphoma: Long term outcomes. Blood. Dec 2014; 124(21).
[10] Younes A, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: A phase 1, open-label, dose-escalation study. The Lancet Oncology. Dec 2013; 14(13):1348-56.
[11] Ansell SM, et al. Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma. Haematologica, suppl. 2. Oct 1, 2013; 98:2.
[12] Ansell SM, et al. Frontline Therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma. Blood. Nov 2012; 120(21):798.
[13] Ansell SM, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL): Echelon-1 study. Journal of Clinical Oncology, Suppl 1. May 2014; 32(15).
[14] Radford J, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin Lymphoma (HL): The Echelon-1 study. Haematologica, Suppl 2. Oct 2013; 98:6-7.
[15] Connors JM, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as frontline treatment for advanced

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	The ongoing Phase I Study SGN35-011 and Phase III Study SGN35-014: Evidence of a manageable safety profile in sequential use with CHOP or in combination with CH-P, Findings of ongoing Phase I Study SGN35-011, an open label, 3-arm study exploring combinations of brentuximab vedotin with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, doxorubicin, and prednisone (CH-P) in patients with treatment-naïve CD30+ mature T-cell and NK cell neoplasms, led to the selection of brentuximab vedotin in combination with CH-P as a regimen for further study. Interim data from the Study SGN35-011 were referenced in the following 2 articles.[17] This Phase I open label study evaluated the safety and activity of brentuximab vedotin administered sequentially with CHOP or in combination with CH-P (CHOP without vincristine) as front-line treatment in patients with CD30+ PTCL. Patients received sequential treatment (once every 3 weeks) with brentuximab vedotin 1.8 mg/kg (2 treatment cycles) followed by CHOP (6 cycles) or brentuximab vedotin 1.8 mg/kg + CH-P (brentuximab vedotin + CH-P) for 6 cycles (once every 3 weeks). Responders received single agent brentuximab vedotin for 8 to 10 additional cycles (total of 16 treatment cycles). Again, both treatment arms in this trial contained brentuximab vedotin plus an alkylator agent (cyclophosphamide) and, therefore, the study lacks a comparator group to evaluate whether the combination was associated with an increased risk. The primary objective of Study SGN35-011 is the assessment of safety. Secondary endpoints include objective response rate (ORR), complete remission (CR) rate, PFS rate, and OS. There are no pre-specified comparisons of the 2 treatment arms. After sequential treatment, 11 (85%) of 13 patients achieved an objective response (CR rate, 62%; estimated 1-year PFS rate, 77%). Grade 3/4 AEs have occurred in 8 (62%) of the 13 treated patients. At the end of combination treatment, all patients (n = 26) have achieved an objective response (CR rate, 88%; estimated 1-year PFS rate, 71%). All 7 patients who did not have anaplastic large-cell lymphoma achieved CR. Grade 3/4 AEs reported in ≥ 10% of patients in the combination treatment group included febrile	

stage classical Hodgkin lymphoma (CHL). The Echelon-1 study. Hematological Oncology, Suppl 1. Jun 2013; 31:278.

[16] Younes A, et al. Phase III study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL). Journal of Clinical Oncology, Suppl. 1. May 2013; 31(15).

[17] Fanale M, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral t-cell lymphomas: Results of a phase I study. J Clin Oncol. 2014;32(28) 3137-43.

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	neutropaenia (31%), neutropaenia (23%), anaemia (15%), and pulmonary embolism (12%). Based on study results, it was concluded that brentuximab vedotin, when administered sequentially with CHOP or in combination with CH-P, had a manageable safety profile and exhibited substantial antitumor activity in newly diagnosed patients with CD30+ PTCL. The data from this study supported the initiation of the company sponsored Phase III Study SGN35-014 that compares brentuximab vedotin + CH-P with CHOP. Study SGN35-014 in patients with mature T cell lymphoma is a randomised, double blind, Phase III study of brentuximab vedotin in combination with CH-P versus CHOP in patients with treatment-naïve CD30+ mature T cell lymphomas.[18] This recently initiated study uses a PFS primary endpoint and is anticipated to complete in 2017. The study is being monitored by an IDMC. No published reports are available at this time. Investigator-initiated Study X25001: Evidence of a manageable safety profile in combination with modified bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimens. Study X25001 is a randomised, Phase II, investigator initiated study, is currently being conducted by the German Hodgkin Study Group to explore combinations of brentuximab vedotin with modified BEACOPP regimens versus escalated BEACOPP. Two experimental regimens are under investigation: brentuximab vedotin plus etoposide, adriamycin, cyclophosphamide, procarbazine, and prednisone (BrECAPP); and brentuximab vedotin plus etoposide, adriamycin, cyclophosphamide, dacarbazine, and dexamethasone (BrECADD). This study is closed to enrolment. The following data [not included in this document] was presented at American Society of Hematology conference in December 2015. *Rationale*: The intensified BEACOPP escalated regimen has substantially improved the survival of advanced stage HL patients. However, the efficacy of this regimen comes along with severe acute toxicities. Brentuximab vedotin is an anti-CD30 directed ADC that has shown very promising single-agent activity and good tolerability in relapsed/refractory HL. Introduction of brentuximab vedotin into the BEACOPP regimen in order to improve its toxicity profile while maintaining its efficacy. *Methods*: Two modified BEACOPP regimens were	

[18] Fanale M, et al.Brentuximab vedotin administered concurrently with multi-agent chemotherapy as frontline treatment of ALCL and other CD30-positive mature T-cell and NK-CELL lymphomas. Blood. Nov 2012; 120(21).

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	developed. In a more conservative variant (BrECAPP), vincristine was replaced by brentuximab vedotin and bleomycin omitted. A more experimental variant (BrECADD) was designed to reduce procarbazine induced gonadal toxicity. Both regimens are administered every 21 days for 6 cycles. This is a randomised Phase II study with the combined primary endpoint being the PET based complete response rate (CRR) after chemotherapy and the complete remission rate (CR/CRu rate) at final restaging including early follow-up for each of the regimens. Safety and feasibility are secondary trial objectives. *Results*: From October 2012 to May 2014, 104 patients have been enrolled and are evaluable for this analysis (52 patients in each treatment arm). Median age is 29 years (range 18 to 60 years), 61% are male, and 83% have Ann Arbor stage III or IV disease. Overall, risk factors were well balanced between the treatment arms and in line with the previous German Hodgkin Study Group (GHSG) studies besides a higher number of patients presenting with large mediastinal mass (40% in each treatment arm). 102 patients qualify for the safety analysis (BrECADD n = 52, BrECAPP n = 50) with two patients not having commenced treatment in the latter group. All 52 patients with BrECADD received the planned number of cycles, 2/50 terminated BrECAPP after 2 and 3 cycles due to toxicity and revision of initial staging by expert panel, respectively. 70% and 60% with complete cycles of BrECADD and BrECAPP received the last treatment cycle at full dose level. The majority of patients did not have treatment delays. 101 patients qualify for the efficacy analysis (BrECADD, n = 52; BrECAPP, n = 49). Complete response rate (CRR) is 88% (95% CI: 77%, 96%) for the BrECADD regimen and 86% (95% CI: 73%, 94%) for BrECAPP with both groups achieving the required number of 42 patients with CRR demanded by the protocol. Regarding the co-primary endpoint CR/CRu, the corresponding rates were 88% for BrECADD (95% CI: 77%, 96%), and 94% (95% CI: 83%, 99%) for BrECAPP. Survival analyses for the BrECADD regimen revealed a PFS of 94% (95% CI: 87%, 100%) at 12 months, and 89% (95% CI: 77%, 100%) at 18 months. Corresponding numbers for BrECAPP were 98% (95% CI: 94%, 100%), and 93% (95% CI: 83%, 100%). OS after a median follow-up time of 18 months for BrECADD was 100%. In the BrECAPP group the median follow-up was 16 months and one patient died. This patient had never received the study treatment. However, this event led to a 1 year OS of	

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	98% (95% CI: 94%, 100%) in the BrECAPP group. Haematological toxicity of Grade 3 or 4 occurred in 42/52 (88%) of BrECADD treated patients, and in 47/50 (96%) with BrECAPP. Main haematotoxicity was leukopenia resulting in 15% (BrECADD) and 8% (BrECAPP) Grade 3 or 4 infections. Organ toxicity of Grade 3 or 4 occurred in 4% of BrECADD treated patients (all events Grade 3), and in 17% in the BrECAPP group (5% Grade 4). Severe neurotoxicity (Grade 3 or 4) was not observed in the BrECADD group and in one patient (2%) in the BrECAPP group (Grade 3 sensory neuropathy). Grade 1 or 2 sensory neuropathy occurred in 35% and 30%, respectively. *Conclusion*: This is the largest study of brentuximab in combination with chemotherapy in the first line treatment of HL reported so far. Both targeted BEACOPP variants are active and well feasible. Based on its superior organ toxicity profile, the sponsor has chosen the BrECADD regimen to challenge the GHSG standard of care escalated BEACOPP for advanced stage HL patients in an international, randomised Phase III study. On the basis of these findings, the MAH believes that contraindication of concomitant chemotherapy is currently warranted only in the instance of bleomycin where clinical evidence suggesting synergistic pulmonary toxicity may exist. The MAH's past and current sponsored clinical research as well as an ongoing investigator-initiated study of the combination use of brentuximab vedotin and intense combination chemotherapy, suggest that most combination uses of brentuximab vedotin studied to date result in manageable safety profiles. Please be advised that there is no evidence that the combined use of brentuximab vedotin (SGN-35) and gemcitabine causes pulmonary toxicity. Pulmonary toxicity has been reported with the combined use of SGN-30 and gemcitabine. SGN-30, the naked (unbound) antibody component of brentuximab vedotin, was investigated separately.[19] While planned study of concomitant brentuximab vedotin and gemcitabine (Study SG035-0002) was not initiated on the basis of pulmonary toxicity findings obtained with the unbound antibody-gemcitabine combination, currently no clinical data exist to substantiate the concern that combining the brentuximab vedotin ADC and gemcitabine results in increased pulmonary toxicity. Preliminary clinical data with the combination of brentuximab vedotin and gemcitabine show a manageable safety profile. Study NCT01780662,	

[19] Blum K, et al. Cancer and Leukemia Group B.Ann Oncol. Serious pulmonary toxicity in patients with Hodgkin's lymphoma with SGN-30, gemcitabine, vinorelbine, and liposomal doxorubicin is associated with an FcγRIIIa-158 V/F polymorphism. 2010 Nov;21(11):2246-54.

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
	entitled 'A Phase I/II study of brentuximab vedotin in combination with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin lymphoma' is an ongoing study conducted by the Children's Oncology Group at the US National Cancer Institute. As also summarised in the sponsor's response to a RMP question from the TGA findings are as follows: *Results*: n = 15 (14 evaluated for haematology); median age 17 years (range: 5 to 28); no dose limiting toxicities (DLT) in 3 patients at dose level 1 (DL1); 2 patients non-haematologocal DLTs at dose level 2 (DL2), both had resolution of all toxicity and continued with brentuximab vedotin at 1.2 mg/kg; expansion cohort of 6 patients enrolled at DL2; no DLTs; Grade 3/4 neutropaenia common (13/14 patients during c1) but self-limited; no Grade 4 non-haem toxicity; no interstitial pneumonitis or pulmonary toxicity attributable to study therapy observed. *Conclusions*: Brentuximab vedotin can be safely given with gemcitabine; the recommended Phase II dose of brentuximab vedotin is 1.8 mg/kg; ongoing Phase II trial will describe CR within 4 cycles.[20]	
8. In the 'Interaction with other Medicines' section, the PI should state that the combined use of brentuximab vedotin and gemcitabine is associated with pulmonary toxicity (or a statement to that effect).	Please be advised that there is no evidence that the combined use of brentuximab vedotin (SGN-35) and gemcitabine causes pulmonary toxicity. Pulmonary toxicity has been reported with the combined use of SGN-30 and gemcitabine. SGN-30, the naked (unbound) antibody component of brentuximab vedotin, was investigated separately.[19] While planned study of concomitant brentuximab vedotin and gemcitabine (Study SG035-0002) was not initiated on the basis of pulmonary toxicity findings obtained with the unbound antibody-gemcitabine combination, currently no clinical data exist to substantiate the concern that combining the brentuximab vedotin ADC and gemcitabine results in increased pulmonary toxicity. Preliminary clinical data with the combination of brentuximab vedotin and gemcitabine show a manageable safety profile. Study NCT01780662, entitled 'A Phase I/II study of brentuximab vedotin (SGN35) in combination with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin lymphoma' is an ongoing study conducted by the Children's Oncology Group at the United US National Cancer Institute.[20] Results and conclusions are as discussed in the answer above.	This is considered acceptable in the context of this application for RMP purposes subject to approval by the Delegate.
9. In the 'Dosage and Administration' section, the	The sponsor maintains that the current dosage and administration instructions, based on the data from	This is considered

[20] Cole P, et al. Phase 1 trial of brentuximab vedotin in combination with gemcitabine for pediatric and young adult patients with relapsed or refractory Hodgkin lymphoma, a Children's Oncology Group report. J Clin Oncol 33, 2015 (suppl; abstr 8544).

Recommendation in RMP report	Sponsor's response	RMP evaluator's comment
sponsor should consider providing dosing information based on body surface area rather than body weight to avoid overdosing or underdosing.	the clinical development program, remains appropriate. The dosage and administration of Adcetris based on body weight is also consistent across all international markets including Europe and North America.	acceptable in the context of this application for RMP purposes subject to approval by the Delegate.
10. It is recommended to the Delegate that the draft consumer medicines information (CMI) document be revised to accommodate the changes made to the product information document.	The sponsor has updated the CMI in accordance with all proposed revisions to the Product Information document.	This is considered acceptable in the context of this application for RMP purposes subject to approval by the Delegate.

Summary of recommendations

'Radiation recall' should be added as an Important Potential Risk in the ASA of the RMP. This should be assigned to Study MA25101 (PASS) and reported in PSURs (reference: based on new recommendation based on Clinical Evaluation Report advice).

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU-RMP Version 5.2 (dated 23 February 2015, DLP 18 August 2014) and Australian-specific annex (ASA) Version 5.0 (dated February 2016), and future updates where TGA approved, as a condition of registration.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type. No changes to the formulation were proposed with this submission.

Advice of the pharmaceutical sub-committee of ACPM was not sought for this submission.

Nonclinical

No new preclinical data was presented.

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

Effect of renal or hepatic impairment

Study SGN35-008b examined the pharmacokinetics of brentuximab vedotin (ADC and MMAE) in a limited number of patients with renal or hepatic impairment in a single cycle of treatment. Eight patients without hepatic or renal impairment served as a control group.

Among the 10 patients with renal impairment studied, 4 patients had mild impairment (CrCl 50 to 80 mL/min), 3 with moderate (CrCl = 30 to 50 mL/min) and 3 with severe (CrCl < 30 mL/min).

Of the seven patients with hepatic impairment studied, 1 patient had mild impairment (Child-Pugh A), 5 with moderate (Child-Pugh B) and one with severe (Child-Pugh C).

MMAE exposure was increased with renal and hepatic impairment and associated with a worse adverse event profile.

The Delegate concurs with the evaluator, and consistent with advice in the FDA approved FDA Label, in that due to the small number of patients studied with each categorisation of hepatic or renal impairment, the conservative recommendations for dosing should be:

- Renal impairment:
  - Mild (creatinine clearance 50 to 80 mL/min): 1.8 mg/kg up to 180 mg
  - Moderate (creatinine clearance 30 to 50 mL/min): 1.2 mg/kg up to 120 mg
  - Severe (creatinine clearance less than 30 mL/min): Avoid use.
- Hepatic impairment:
  - Mild (Child-Pugh A): 1.2 mg/kg up to 120 mg
  - Moderate (Child-Pugh B) or severe (Child-Pugh C): Avoid use.

Drug-drug interactions

The currently approved PI documents:

1. A contraindication for the use of Adcetris and bleomycin owing to pulmonary toxicity
2. An increase in MMAE exposure (around 73%) when Adcetris is concomitantly administered with ketoconazole, leading to an increased risk of neutropaenia
3. Co-administration of Adcetris and rifampicin reduces exposure of MMAE by approximately 31%.

Evaluation of Study SGN35-008a and the exploratory analysis of adverse events arising from Study SGN35-005 did not provide any additional data to update the information contained in the PI.

Anti-drug antibody (Anti-therapeutic antibody) assessment

Two assays have been employed to assess the development of ATA. Both assays are observed to have yielded positive results for previously-unexposed patients, with a

specificity reported by the sponsor of 6.5% for patients in Study SGN35-005. The evaluator has commented on the test characteristics being not entirely suitable of determining ATA status, given the proportion of patients who were found to have false positive results.

No new information was presented regarding the effect of ATA on efficacy or safety, and hence no update to the information already contained in the PI is recommended.

Pharmacodynamic effects

No new data was presented for evaluation.

Efficacy

A single pivotal study was presented for evaluation, Study SGN35-005 (AETHERA).

This was a randomised, double blind, placebo controlled Phase III study of brentuximab vedotin and BSC versus placebo and BSC in the treatment of patients at high risk of residual HL following ASCT.

Patients who had received an ASCT for HL in the previous 30 to 45 days were assessed for eligibility according to the presence of risk factors prior to ASCT and the response to salvage therapy. Patients with progressive disease after salvage therapy were excluded from the study.

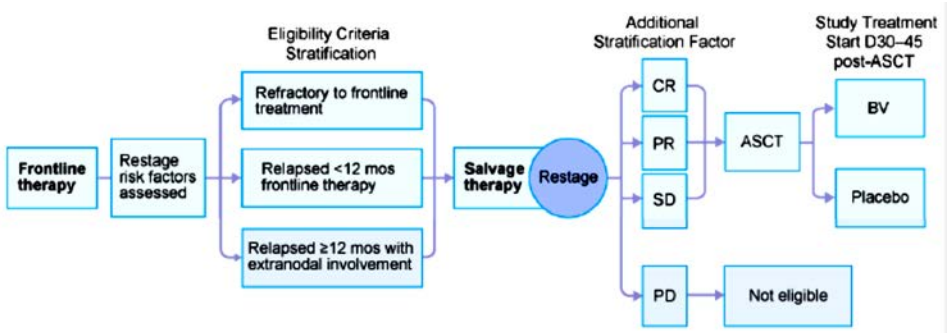
329 patients were randomised: 165 in the brentuximab vedotin arm; 164 in the placebo arm. Baseline patient characteristics were balanced between the study arms.

Randomisation was stratified by eligibility criteria and response to salvage chemotherapy prior to ASCT:

- Refractory/relapsed status after the end of frontline standard chemotherapy or a combined modality treatment program:
  - Any refractory HL
  - Relapsed HL that occurred < 12 months after the end of frontline therapy
  - Relapsed HL that occurred ≥ 12 months after the end of frontline therapy (with this defined as also having extra-nodal involvement at the time of pre-ASCT relapse).
- Best clinical response, according to the Revised Response Criteria for Malignant Lymphoma, achieved after completion of salvage therapy prior to ASCT:
  - Complete response (CR)
  - Partial response (PR)
  - Stable disease (SD).

The study design is shown in Figure 6, below.

Figure 6. Study SGN35-005 design



Abbreviations: ASCT = autologous stem cell transplant; BV = brentuximab vedotin; CR = complete remission; PD = progressive disease; PR = partial remission; SD = stable disease

Randomisation according to stratification factors was balanced between the two treatment arms.

Patients received brentuximab vedotin 1.8 mg/kg or placebo, administered as a single outpatient IV infusion on Day 1 of each 21 day cycle, to a maximum of 16 cycles. Cross-over was permitted for patients with investigator-confirmed progressive disease.

Reasons for study discontinuation were similar between treatment arms, whereas reasons for study treatment discontinuation were dissimilar. AEs were more common among those receiving brentuximab, while disease progression was more common in the placebo arm.

Pre-specified risk factors for disease progression were:

- Refractory/relapsed status after the end of frontline standard chemotherapy or a combined modality treatment program (refractory HL, relapsed HL that occurred < 12 months, and relapsed HL that occurred ≥ 12 months).
- Best response of CR, PR or SD after the completion of salvage therapy prior to ASCT, as assessed by the investigator.
- Extra-nodal disease at the time of pre-ASCT relapse (yes/no).
- Number of treatments (frontline and salvage) prior to ASCT (2, > 2).
- B symptoms after failure of frontline therapy (yes/no).
- PET status prior to ASCT (positive or negative).

Primary outcome

PFS was the primary outcome.

The median follow-up time from randomisation to the primary efficacy analysis was 22.1 months (range: 0 to 49).

The median PFS, assessed by independent review, for patients who received brentuximab vedotin was 42.9 months (95% CI 30.4, 42.9) and the median PFS for patients who received placebo was 24.1 months (95% CI 11.5, (upper limit not defined)). The difference between the 2 arms was statistically significant in favour of brentuximab vedotin; stratified HR 0.57 (95% CI 0.40, 0.81), p = 0.001.

Secondary outcomes

Multiple methods of assessing PFS were reported as secondary outcomes.

Investigator-assessed PFS differed from the independently determined PFS owing to the use of non-scheduled patient investigations. Consequently, the stratified hazard ratio of PFS was used, as shown below in Table 6.

Table 6. Stratified hazard ratio of PFS

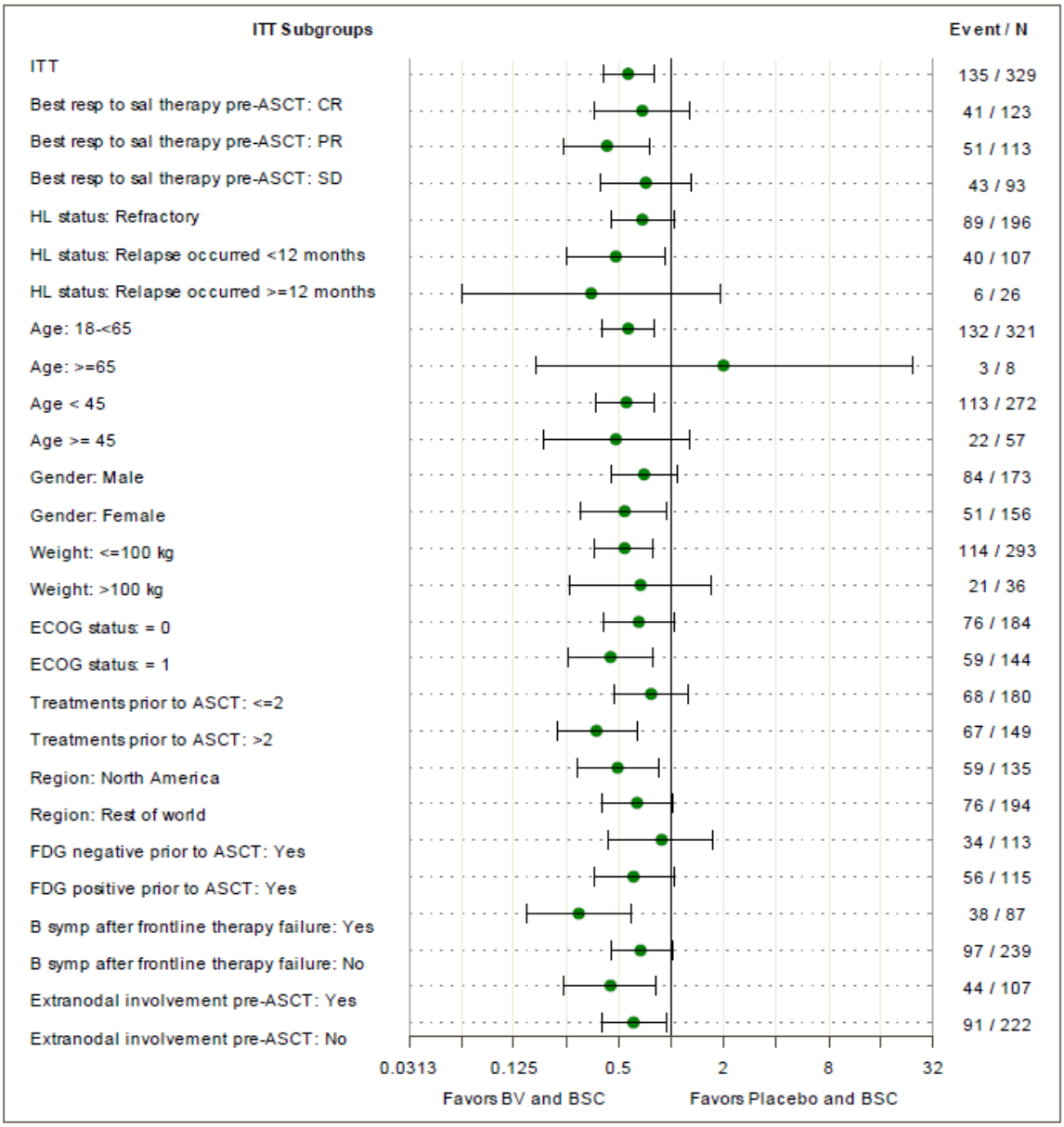
	Stratified hazard ratio of PFS	Median PFS, months (95%CI)	
		Placebo	Brentuximab vedotin
Investigator-assessed	0.5 (95% CI 0.36, 0.70)	15.8 (8.5, -)	- (26.4, -)
IRF Per-protocol population	0.45 (95% CI 0.30, 0.68)	17.8 (6.5, -)	Not reached (30.4, -)
IRF using EMA censoring guidelines	0.55 (95% CI 0.39, 0.77)	24.1 (11.5, -)	39.9 (30.4, 42.9)

Note: Missing CI relate that upper/lower bounds could not be estimated.

Pre-specified and post-hoc subgroup analysis of PFS

The pre-specified analysis of PFS is shown below in Figure 7.

Figure 7. Progression-free survival by prognostic factors and other patient characteristics



For any risk category with two or fewer events, the hazard ratio and confidence intervals are not displayed.
Stratified hazard ratios are presented, with the exception of stratification factors for which the unstratified hazard ratios are presented. Analyses are based on randomized stratum.

Estimated median duration of PFS according to risk factors is shown below in Table 7.

Table 7. Study SGN35-005 subgroups and median progression survival

Risk factor for progressive disease following ASCT for HL	Median PFS by IRF in months (95% CI)	
	Placebo[1]	Brentuximab vedotin[1]
Low risk for progression		
2 treatment lines prior to ASCT	Not yet reached (12.3, —)	34.3 (24.8, —)

Risk factor for progressive disease following ASCT for HL	Median PFS by IRF in months (95% CI)	
	Placebo[1]	Brentuximab vedotin[1]
PET-negative prior to ASCT	Not yet reached (18.0, —)	42.9 (34.3, 42.9)
no B symptoms at the time of relapse prior to ASCT	Not yet reached (12.0, —)	34.3 (26.4, —)
Complete response to salvage therapy	Not yet reached (23.7, —)	42.9 (34.3, 42.9)
High risk for progression		
Refractory disease after frontline therapy	17.8 (6.0, —)	30.4 (18.0, —)
> 2 treatment lines prior to ASCT	7.1 (3.3, 15.3)	Not yet reached (26.4, —)
B symptoms at the time of relapse prior to ASCT	12.3 (3.1, 24.5)	42.9 (18.0, 42.9)
PET positive prior to ASCT	12.0 (3.1, —)	30.4 (13.9, —)
Partial response to salvage therapy	12.0 (3.3, —)	Not yet reached (26.4, —)
≥ 3 risk factors	7.1 (3.3, 17.8)	Not yet reached (18.0, —)

For the prognostic factors associated with 'low risk' for disease progression, the placebo group may have an improved PFS outcome compared to those who received brentuximab vedotin. However, there is no formal statistical analysis presented to test this.

Conversely, for the prognostic factors associated with 'high risk' of disease progression, there may be a benefit for those patients who received brentuximab vedotin.

The post-hoc analysis of PFS according to number of risk factors is shown below in Table 8.

Table 8. Post-hoc analysis of PFS according to number of risk factors

	≥1 Risk Factor		≥2 Risk Factors		≥3 Risk Factors	
	Placebo (N=164) n (%)	BV (N=165) n (%)	Placebo (N=136) n (%)	BV (N=144) n (%)	Placebo (N=84) n (%)	BV (N=82) n (%)
Patients with PFS event	75 (46)	60 (36)	68 (50)	51 (35)	49 (58)	32 (39)
Estimated progression-free rate[a] at						
12 months (95% CI)[b]	57% (48%, 64%)	76% (68%, 82%)	52% (43%,60%)	75% (67%,82%)	45% (33%,56%)	71% (59%,80%)
24 months (95% CI)[b]	51% (43%, 59%)	63% (55% 70%)	45% (36% 54%)	64% (56% 72%)	34% (23%,46%)	60% (48%,70%)
Median PFS (months) (95% CI)[b]	24.1 (11.5, -)	42.9 (30.4, 42.9)	12.3 (6.2, -)	42.9 (30.4, 42.9)	7.1 (3.3, 17.8)	- (18.0, -)
Stratified Hazard Ratio[c,d] (95% CI)[c]		0.571 (0.404, 0.808)		0.488 (0.337, 0.706)		0.433 (0.274, 0.683)

a As estimated using Kaplan-Meier methods.
b Calculated using the complementary log-log transformation method (Collett, 1994).
c Hazard ratio (HR) comparing brentuximab vedotin (BV) with placebo. A HR < 1.0 indicates a lower average event rate and a longer survival time for the BV arm relative to the placebo arm.
d Computed using stratification factors (Best response [Cheson 2007] to Salvage Therapy pre-ASCT and HL status) at randomization.

Of note, the stratified hazard ratio of PFS favours treatment with brentuximab vedotin irrespective of number of categorised risk factors.

Among patients allocated to placebo, approximately half (85/154, 55%) required subsequent therapy for disease progression. For those with no requirement for additional therapy, owing to ASCT success, the median PFS was 30.9 months.

The analysis of PFS according to IRF by the number of risk factors is limited by the number of patients in each subgroup and immaturity of the data.

The analysis of OS according to number of risk factors cannot be satisfactorily interpreted for registration purposes owing to the small number of patients in each sub-group and potential for post-progression treatment cross-over.

The estimate of median duration of OS could not be estimated in either arm. The immature data presented reveals no survival advantage to brentuximab vedotin use, even with a statistical analysis taking treatment cross-over into consideration.

OS assessed according to number of risk factors shows no subgroup with a benefit from treatment.

Quality of life assessments

As assessed, by the standardised test EQ-5D, whilst there was no apparent improvement in patient-reported outcomes, there was also no apparent worsening of patient reported outcomes among the arm receiving brentuximab vedotin as compared to placebo. However, the evaluator states that the lack of difference may be attributable to the effect of treatment cross-over.

For patients who experienced on-study disease progression, there was a not unexpected divergence of patient reported outcomes, worse for those with progression.

Safety in the proposed indication

Safety was reported for Study SGN35-005 and from six PSURs. Furthermore, in the sponsors response to TGA's questions, further safety data was referred to, which was evaluated as a separate safety related request.

The proportion of patients who completed 16 cycles of study treatment in Study SGN35-005 were not substantially different between treatment arms, 78/165 (47%) patients in the brentuximab vedotin arm and 81/164 (49%) in the placebo arm. The median number of treatment cycles in each arm was 15 cycles (range 1 to 16).

The most common reason for premature cessation of study treatment in the brentuximab vedotin arm was adverse events and in the placebo arm, progressive disease.

Dose reductions and delays were more commonly observed in the brentuximab vedotin arm with peripheral sensory or motor neuropathies the most frequently reported AEs leading to dose reduction (46 patients), as shown below in Table 9.

Table 9. Dose modification by patient

	Placebo (N=160) n (%)	Brentuximab Vedotin (N=167) n (%)	Total (N=327) n (%)
Dose delayed for per-protocol reasons	41 (26)	90 (54)	131 (40)
Dose reduced for per-protocol reasons	4 (3)	53 (32)	57 (17)
Unplanned dose adjustment or infusion interruption			
Infusion interrupted due to adverse event	1 (1)	6 (4)	7 (2)
Infusion stopped early due to adverse event	0	6 (4)	6 (2)
Dose error not leading to interruption or stoppage	7 (4)	3 (2)	10 (3)

Note: Any portion of a dose received was captured as 1 dose.

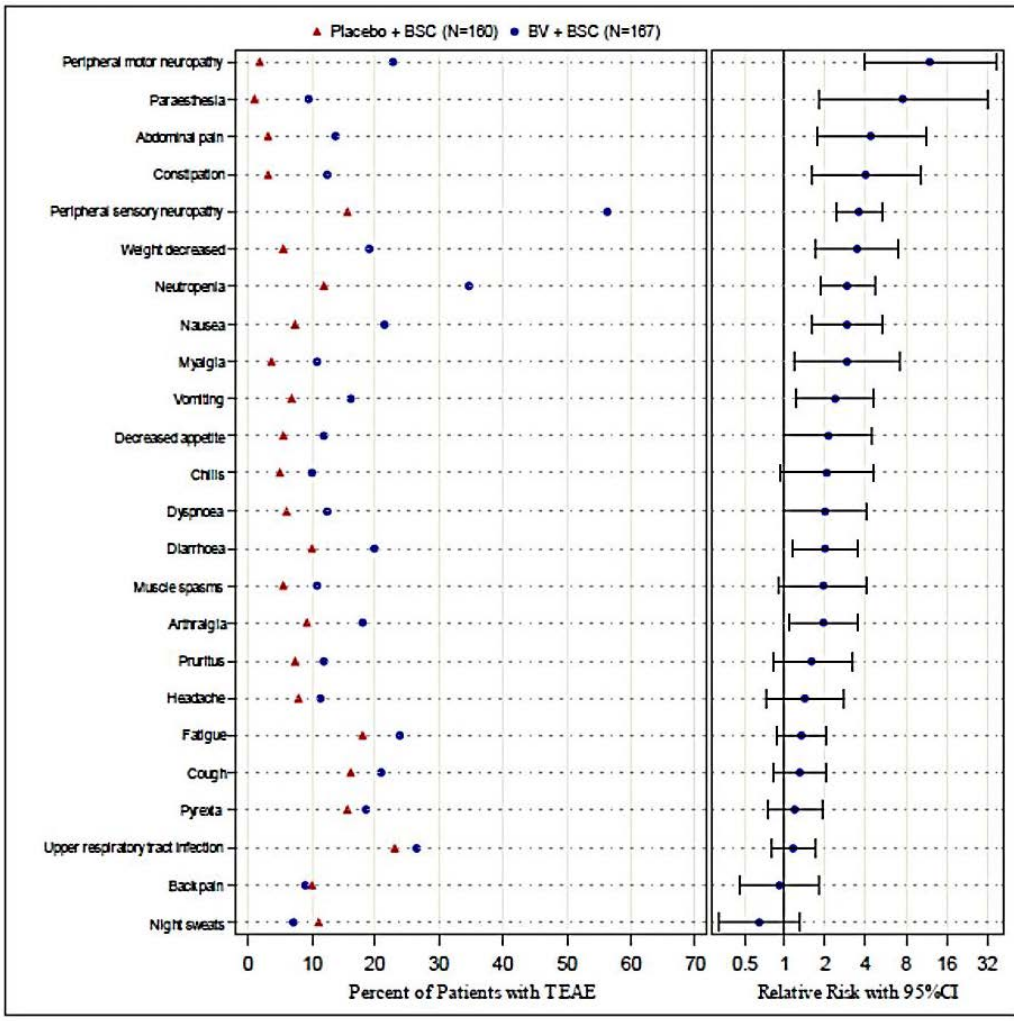
General AEs reported from study Day 1, before administration of the first dose of study treatment, through to Day 30 post-treatment cessation occurred in 163 (98%) patients in the brentuximab vedotin arm and 142 (89%) in the placebo arm.

AEs occurring in the patients who were initially randomised to placebo, but subsequently received brentuximab vedotin following disease progression were not reported. This usage is consistent with the currently approved indication.

The incidence of treatment related AEs was discrepant, 88% of the AEs in the brentuximab vedotin arm were assessed as treatment related, compared to 49% of those in the placebo arm. The most common of these Grade 3 or higher AEs were neutropaenia (49 patients; 29%), peripheral sensory neuropathy (17 patients; 10%), and peripheral motor neuropathy (10 patients; 6%). A total of 21 (13%) patients in the brentuximab vedotin arm and 10 patients (6%) in the placebo arm had Grade 4 AEs. The most common Grade 4 event was neutropaenia, which occurred in 12 patients (7%) in the brentuximab vedotin arm and 6 patients (4%) in the placebo arm. The only other Grade 4 AE reported in more than 1 patient in either treatment arm was thrombocytopaenia, which occurred in 4 patients (2%) in the brentuximab vedotin arm and 3 patients (2%) in the placebo arm.

The relative risk of specific TEAEs is shown below in Figure 8.

Figure 8. Treatment emergent adverse events in ≥ 10% of patients in either treatment arm



BV: brentuximab vedotin. Events are sorted by relative risk; a relative risk <1 means reduced risk for brentuximab vedotin, while a relative risk >1 means increased risk for brentuximab vedotin.

Treatment-related deaths were uncommon among the study population, occurring in 2 patients (1%) in the placebo arm and 5 patients (3%) in the brentuximab vedotin arm.

Adverse events of special interest

AEs of special interest for the current submission are outlined below:

Peripheral neuropathy

Predominately owing to the effects of prior therapy, peripheral neuropathy was present in 41% in the brentuximab vedotin arm and 34% in the placebo arm. Among those in the brentuximab arm, neuropathy worsened in severity post-baseline in 25 patients but later returned to baseline in 19 patients.

Post-marketing experience of peripheral neuropathy, as per the most recent PSUR, documents 1398 (47%) patients with peripheral neuropathy as a TEAE in the clinical trials programme. Of these 32 were reported as SAEs; 189 were Grade 3 or 4 events, 1358 were Grade 1 or 2 events and there were no fatal outcomes. There had been another 128 SAEs reported from other sources. Of these, 15 were considered to be Grade 3 or 4 in severity and there were 2 with fatal outcome.

Pulmonary toxicity (new entry in the PI)

Grade 3 to 5 events occurred in 4 patients (2%) of those in the brentuximab vedotin arm as compared to 2 patients (1.2%) in the placebo arm.

Infusion-related reactions

Causally-related infusion-related reactions occurred in 25 patients in the brentuximab vedotin arm; there were no reported event of anaphylaxis or events worse than Grade 3. The PI contains advice regarding patient management following an IRR, this remains satisfactory given the current data.

Serious and opportunistic infections

Such events are already described in the PI. In the current study there was an imbalance in the proportion of patients experiencing serious events, with a greater incidence in those receiving brentuximab vedotin.

Haematological toxicity

Neutropaenia occurred in 58 patients (35%) in the brentuximab vedotin arm and 19 patients (12%) in the placebo arm. In the brentuximab vedotin arm, Grade 3 neutropenia was reported in 37 patients (22%), Grade 4 neutropaenia was reported in 12 patients (7%) and there was a single case of non-serious, treatment-related febrile neutropaenia.

Thrombocytopaenia of any grade was reported in 12 patients (7%) in the brentuximab vedotin arm and 5 patients (3%) in the placebo arm. In the brentuximab vedotin arm, Grade 3 thrombocytopaenia was reported in 3 patients and Grade 4 was reported in 4 patients. Thrombocytopaenia led to a dose delay for 3 patients in the brentuximab vedotin arm and 1 patient from each treatment group had treatment discontinued due to thrombocytopaenia.

Anaemia of any grade was reported in 14 patients (8%) in the brentuximab vedotin arm (Grade 3 in 6 patients) and 4 patients (3%) in the placebo arm. No Grade 4 anaemia, dose delay or treatment discontinuation due to anaemia was reported in either treatment arm.

Hyperglycaemia

Among the 5 patients in the brentuximab arm who were reported to have hyperglycaemia, all had pre-existing risk factors. Resolution of hyperglycaemia was observed in 3 of the 5 patients.

Hepatotoxicity

Grade 3 or higher events were reported for 7 patients (4%) in the brentuximab vedotin arm and 4 patients (3%) in the placebo arm. Hepatotoxicity SAEs were reported for 3 patients in the brentuximab vedotin arm and 2 patients in the placebo arm.

Post-marketing experience reveals the risk of hepatotoxicity to be highest during cycles 1 to 2, with the majority of events being of Grade 1 or 2 (756%); Grades 3 or 4 events were reported for 140 patients (22% of all hepatotoxicity events).

The clinical evaluator recommends amendment to the PI regarding hepatotoxicity events.

Immunogenicity

As discussed above, the imprecision of the assay used to determine anti-drug antibody status was evaluated as being an impairment to guide the clinical implementation of brentuximab vedotin.

Risk management plan

The advice of the Advisory Committee on the Safety of Medicines (ACSOM) was not sought for this submission.

The RMP was evaluated to the satisfaction of the evaluator, with no outstanding issues for the Delegate to consider.

Risk-benefit analysis

Delegate's considerations

Efficacy and safety

The pivotal study demonstrates an advantage for reducing the risk of disease progression in patients with HL who have received induction chemotherapy and an ASCT. This result does not however mean that all patients should receive this consolidation regimen owing to the variable risk of disease progression, nor did all patients obtain a complete and durable response. Of the 165 patients who received brentuximab vedotin, 24 (14.5%) developed disease progression; it cannot be conclusively determined if these patients had the 'highest' risk of relapse. The risk for disease progression post-HSCT may be a continuum but has only been delineated by the categorised risk-factors currently identifiable. The challenge is to satisfactorily identify the level of risk for those patients who may benefit from consolidation therapy from those who will receive no benefit, or potentially be harmed by it. The current submission does not demonstrate an absolute level of acceptable or unacceptable risk.

The pre-specified risk factors (for example, time to refractory/relapsed status after the end of frontline standard chemotherapy) for disease progression, by their clinical utility, are variables which have been categorised that may be more appropriate to be expressed continuously. It is known that dichotomisation of variables reduces the power of a study to detect a relationship between a variable and patient outcome.[21,22] For the current study, the ability to determine the patients who may benefit from consolidation therapy with brentuximab vedotin is therefore made more complex as a result.

In order to identify a group of patients who may not benefit from consolidation, the risk of disease progression would have to be negligible in this group.

The background risk of disease progression for study entrants was evident, whereby 55% of the placebo group experienced disease progression. The treatment of these patients who progressed is fulfilled by the currently approved indication for brentuximab vedotin.

There are insufficient numbers of patients in the categorisation of risk of relapse/disease progression to be satisfied that the indication can be targeted to a particular level of risk.

Treatment cross-over has the effect of minimising the apparent difference in efficacy between the active and control treatments and also to exaggerate the difference in safety between the two arms. The lack of difference in patient reported outcomes is reassuring in that the 'true' difference between the treatment arms, that is, without cross-over, would be likely to remain without a difference or in favour of brentuximab vedotin, rather than demonstrating superiority of placebo.

The effect of incomplete consolidation therapy with brentuximab vedotin on risk of developing disease progression is uncertain. Premature discontinuation of study therapy occurred in 54/164 (33%) of those initially randomised to brentuximab vedotin. The

[21] Altman D, et al. The cost of dichotomising continuous variables. BMJ 2006 May 6; 332(7549):1080
[22] Haynes R, et al. Clinical epidemiology. P. 2006 (third edition). Lippincott Williams & Wilkins

subsequent outcomes such as severity of relapse and response to additional therapy for these patients have not been presented.

Despite the evidence presented in the dossier, the decision to treat an individual patient with a discrete number of risk factors for disease progression following HSCT with brentuximab vedotin will remain a complex one, and one which requires the provision of information of sufficient calibre to obtain informed consent by specialist physicians. In recommending the indication below, the Delegate considers that patients with increased risk for relapse, who have limited treatment options, are provided the opportunity to receive brentuximab vedotin. There has to be the appreciation that consolidation treatment does not completely abolish the risk of relapse; that it will likely be accompanied by adverse events whether or not a benefit is derived; that no effect on long-term survival has been demonstrated and that premature discontinuation of consolidation therapy has unknown risks for the success of future therapy.

Dose

The proposed dose is considered acceptable for the proposed usage.

Indication

Owing to the numerical size of the subgroups according to number of risk factors, and the consequent imprecision of the efficacy outcomes, the Delegate considers that the efficacy data presented in the dossier is not sufficiently robust to specify the degree of risk for relapse that can be categorically documented in the indication.

The registration of brentuximab vedotin for the treatment of patients who are at increased risk of disease progression is not mandatory for all potential patients, but only an option for those who, after a discussion regarding informed consent for treatment, it is considered appropriate.

In addition, the clinical evaluator recommended the inclusion of two additional sentences in the indication:

> *'This indication was approved based on promising progression free survival in a placebo controlled trial. The data did not demonstrate an increased survival or improved quality of life with Adcetris.'*

The Delegate considers that a statement for the indication regarding data limitations should be reserved for submissions that are designed for provisional approval pathways. The demonstration of PFS benefit from the pivotal study is not 'promising' but a real finding. Furthermore, while there was no demonstrated improvement, there was no material difference in quality of life assessment scores between the active and placebo arms of the pivotal study.

What is missing from the data is the demonstration of a beneficial effect on overall survival. In order for clinicians to satisfactorily obtain informed consent, a reference to the lack of overall survival data in this 'at risk' population remains pertinent and should be included in the indication in the PI *and* CMI.

The Delegate therefore proposes the following indication:

> *'Treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.*
>
> *This indication is based upon an improvement in progression-free survival only; no improvement in overall survival has been demonstrated.'*

Deficiencies of the data

An improvement in overall survival has not been demonstrated. It remains unlikely that in the event of submission approval, the usage of brentuximab vedotin outside of a clinical

trial will be able to demonstrate the unbiased magnitude of survival as patients that are deemed at increased risk and who do not receive consolidation therapy will consequently receive brentuximab vedotin upon relapse.

Indeed, there are planned or active trials (as seen on Clinicaltrials.gov; 29 June 2016) investigating the use of brentuximab vedotin pre-ASCT, in combination with numerous other therapies (including but not limited to rituximab, ipilimumab and nivolumab) which may render the use of monotherapy brentuximab vedotin, in patients with increased risk of relapse, redundant.

The risks to patients who receive brentuximab vedotin but who prematurely cease therapy owing to adverse events have not been established. It is uncertain if such patients, who later go on to experience disease progression, will obtain an efficacy benefit from brentuximab vedotin and what the magnitude of this effect may be.

Proposed regulatory action

The Delegate considers the submission to extend the indications of brentuximab vedotin to have sufficiently demonstrated efficacy and safety in order to be registered in the proposed usage.

The clinical evaluator recommended that a registry be set up for future patients to further inform the outcomes of patients receiving post-HSCT brentuximab vedotin. The Delegate does not consider a patient registry necessary since the submission is sufficient to register an extension of indications and is not predicated upon the submission of further data.

Provision of a healthcare professional information brochure was also recommended by the clinical evaluator. This is also considered not required, as the PI and CMI are being updated with this submission.

The Delegate considers it prudent for the sponsor to produce a patient safety card for patients at risk of disease progression, given that these patients are being treated in a prophylactic manner, the major risks of treatment need to be clearly identifiable. The risks of brentuximab vedotin in a fitter population of patients, while not substantially different from those already described, mean that they are more likely to present to non-specialist centres where attending staff are unlikely to be familiar with the adverse event profile of brentuximab vedotin. Such a patient safety card will supplement the information in the CMI and serve to minimise risks to patients.

Conditions of registration

As per the RMP evaluator:

> *Implement EU-RMP Version 5.2 (dated 23 February 2015, DLP 18 August 2014) and Australian-specific annex (ASA) Version 5.0 (dated February 2016), and future updates where TGA approved, as a condition of registration.*

Summary of issues

- The amendment to the indication moves treatment of patients with established relapsed/refractory HL to an earlier phase of those at risk of relapse or progression.
- The orphan nature of the disease makes determination of the patient population that has the greatest risk, among those with 'increased' risk, of relapse which may benefit from brentuximab vedotin following HSCT difficult.
- Conversely, there is no categorical definition as to which patients at 'increased' risk of disease progression should not receive consolidation therapy with brentuximab vedotin.

- Efficacy was demonstrated by progression-free survival. No effect on overall survival has been reported in the pivotal study.
- Adverse effects from consolidation use are consistent with those already known, albeit with varying incidence.
- Effects of partial treatment of those with 'increased' risk are not established.
- A separate safety-related request was evaluated and incorporated into the clinical evaluation regarding events of pulmonary toxicity, hepatotoxicity and GI toxicity.

Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved for registration.

Request for ACPM advice

1. Given the limitation of the patient population, does the committee consider there sufficient data to specify a degree of risk of relapse of disease progression which can be specified in the indication?
2. Does the committee consider there to be a population of patients who should not receive consolidation brentuximab post-HSCT?
3. What is the opinion of the committee regarding the provision of a patient safety card to those patients 'at risk' of relapse or disease progression?

Response from sponsor

Unmet clinical need

The SGN35-005 (AETHERA) trial was conducted in patients with HL following ASCT. Currently, this treatment setting is managed through watchful waiting. ASCT is used with curative intent, and it is understood that approximately half of HL cases might be cured without further therapy. Yet in the other cases, HL will return with devastating consequences for these typically young and otherwise productive patients who have endured previous aggressive and invasive therapy. Historically, relapse in this setting is associated with a median post-progression survival of only 1.3 years.[23,24] The AETHERA study demonstrated that Adcetris treatment produced a statistically significant benefit in PFS. PFS was selected as the primary endpoint of the study because it represents a clinically relevant measure of benefit in this population of patients who are typically in a very productive and responsible phase of their careers and personal lives. For these patients, delaying or preventing relapse is an important treatment goal, and as will be shown in the analyses that follow, this PFS benefit can translate to other objective measures of clinical benefit.

Failure to attain a cure in HL is noted as a burden for patients and caregivers. In the current HL treatment paradigm, despite the advantages offered by Adcetris in the relapsed or refractory setting, ASCT represents patients' last and best chance of cure. Among all patients requiring ASCT for HL, 50% of patients, cure will not be attained with ASCT alone.[23,24] For those whose disease is not cured, the human cost is high. As described by the AETHERA principal investigator from their experience at the Memorial Sloan Kettering

[23] Arai S, et al. Defining a Hodgkin Lymphoma Population for Novel Therapeutics after Relapse from Autologous Hematopoietic Cell Transplantation. Leukemia & Lymphoma (2013) 54:2531-3.
[24] von Tresckow B, et al. Outcome and risk factors of patients with Hodgkin Lymphoma who relapse or progress after autologous stem cell transplant. Leukemia & Lymphoma (2014); 55: 1922-4.

Cancer Center, the remainder of these young patients' lives becomes focused around their treatment. Typical patients with refractory or recurrent disease post ASCT receive a median of 5 investigational agents, without long breaks between those agents, prior to their deaths before age 40 (personal communication dated 5 May 2015). As illustrated by the AETHERA data, approximately 55% of placebo patients at increased risk of relapse were not cured by ASCT alone, as opposed to approximately 35% of patients receiving consolidation treatment with Adcetris (PFS per investigator with clinical lymphoma assessments beyond 24 months to define events and censor patients who had not yet progressed). The analysis of PFS per investigator including clinical lymphoma assessments demonstrates that each arm appears to have reached a stable plateau beyond 24 months with marked separation between the curves. This analysis yielded a stratified HR of 0.50 (95% CI (0.36, 0.70)). The 55% of placebo patients with disease progression in the plateau phase represents a greater proportion than the 50% it is expected will not be cured by ASCT alone, suggesting that patients risk factors for relapse or progression present a higher unmet medical need. Further, in the relapsed or refractory setting post ASCT, despite the use of Adcetris to extend such patients' lives, very few can be cured.

Long-term follow-up of Study SG035-0003: The earlier clinical investigation in patients with HL that had been refractory to or relapsed after ASCT (Study SG035-0003) suggests that Adcetris delays but does not ultimately prevent disease progression or death in most patients who receive the drug later in their treatment course. At the time of termination of Study SG035-0003, the estimated 5 year investigator-assessed PFS rate was 22% and the estimated 5 year OS rate per Kaplan-Meier analysis was 41% (Study SG035-0003 Clinical Study Report, Addendum 2). This study's finding of a median OS duration of 40.5 months in the relapsed or refractory setting also corroborates the likelihood that the AETHERA OS data will remain immature for years to come. Ultimately at the time of closure of the Study SG035-0003 study, 15 of its 102 patients (15%) were known to be in remission. The majority of these patients with sustained remissions (13 of 15 patients with sustained remissions, 87%) had attained a CR with initial Adcetris treatment. These data illustrate that achieving complete remission is of vital importance to curing HL and to patients' long-term survival (Study SG035-0003 Clinical Study Report Addendum 2). Further, of these 15 patients still alive and in remission at study closure, 6 patients (40%) had received a later consolidative allogeneic stem cell transplant. Thus, in the treatment of relapsed or recurrent HL, Adcetris alone does not result in cure in > 90% of patients. The very poor prognosis for patients with HL that returns post ASCT underscores the vital importance of increasing cure rates earlier in therapy.[25]

Analysis for delay of next subsequent therapy: In this post-hoc analysis of TTNT, investigator-reported receipt of therapy for HL subsequent to placebo (placebo arm) or Adcetris (brentuximab vedotin arm) was considered a TTNT event. Patients without a TTNT event were censored at the date of their last follow-up. Fifty-one patients randomized to Adcetris (31%) received subsequent therapy versus 85 patients (52%) randomized to placebo (HR = 0.448). This effect appeared durable, with an estimated 36 month subsequent therapy-free rate of 65.6% for patients randomized to Adcetris versus 45.8% for patients randomised to placebo. The results of this TTNT analysis show a strong and sustained trend for a reduced risk of receiving subsequent therapy in patients receiving Adcetris. This analysis, although not pre-specified, yielded a positive HR (0.45, 95% CI 0.32, 0.64). After enduring the frontline and salvage therapies, pre-transplantation conditioning regimen, and stem cell transplantation typical of the previous treatments in this setting, achieving sustained remission without the need for further therapy is undoubtedly a meaningful outcome for patients.

[25] Chen R, et al. Five-Year Survival Data Demonstrating Durable Responses from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma. Poster. American Society of Hematology Annual Meeting (2015). Orlando, FL; December 2015.

The majority of patients who are not cured by ASCT alone face further disease progression, treatment, and eventually HL-related death. Consolidation therapy with Adcetris offers sustained PFS, and the potential for cure, to approximately 20% more patients, of crucial benefit in this setting where the return of HL is usually repeated until it results in death. Moreover, this clinical benefit is also evidenced by a prolonged time to next therapy. Taken together, these data suggest that post-ASCT consolidation with Adcetris reduces the need for further treatment and offers better outcomes than watchful waiting.

Use in renal and hepatic impairment

The sponsor disagrees with the Delegate's proposed revisions to the Dosage and Administration section of the Adcetris PI, which would lower the recommended starting dose for patients with moderate renal impairment and preclude treatment of patients with severe renal impairment and patients with moderate to severe hepatic impairment in the setting of active lymphoma.

The sponsor acknowledges that a small sample of patients comprise the dataset supporting the use of brentuximab vedotin in patients with renal and hepatic impairment. However, the previously agreed starting dose and guidelines for use in the setting of active lymphoma remain relevant for patients with active disease. For such patients, brentuximab vedotin represents an important treatment option that, subject to clinical judgment and a careful evaluation of benefit to risk ratio, should be available to patients for whom effective treatment options are few. For these patients, the sponsor recommends retaining the dosage and administration guidelines currently stated within the Adcetris PI. Of note, these recommendations are consistent with those approved in the EU as presented in the SmPC. Data summaries [from previous Adcetris submissions to the TGA] underlie the current recommendations for patients with relapsed or refractory (active) lymphoma.

Renal Impairment: In Study SGN35-008 Part B, brentuximab vedotin was given at a starting dose of 1.2 mg/kg. Severe renal impairment (n = 3) was associated with increased MMAE exposures. Mild or moderate renal impairment (n = 6) did not meaningfully change the pharmacokinetics of MMAE. Further, patients with mild (CrCL > 50 to 80 mL/min) and moderate (CrCL 30 to 50 mL/min) renal impairment were permitted to enrol in pivotal Studies SG035-0003 and SG035-0004, received a starting dose of 1.8 mg/kg brentuximab vedotin, and did not experience an appreciably altered safety profile compared with patients with normal kidney function. It is thus recommended that only patients with severe renal impairment receive a reduced starting dose of 1.2 mg/kg brentuximab vedotin.

Hepatic Impairment: At a reduced dose of 1.2 mg/kg brentuximab vedotin, MMAE exposure data in patients with hepatic impairment suggest the possibility of a somewhat increased risk of adverse events whereas corresponding ADC exposures suggest a potential for slight decreases in efficacy, However, the relapsed and refractory patient population has no alternative treatment option that has shown efficacy remotely as high as was demonstrated by brentuximab vedotin. Brentuximab vedotin at 1.2 mg/kg thus appears to be a treatment option that remains clinically useful for patients with active lymphoma and no other treatment options.

The sponsor agrees to restrict use in patients with severe renal impairment and in patients with moderate or severe hepatic impairment to patients with 'active disease and no other treatment options.' The sponsor has revised the text included in both the 'Precautions' and 'Dosage and Administration' sections of the Adcetris PI to more explicitly inform the treating physician that the data are limited, monitoring and oversight are required, and that use in patients with severe renal impairment and use in patients with

moderate or severe hepatic impairment is restricted to patients with 'active disease and no other treatment options'.

Patient safety card

The sponsor notes the Delegate's comments regarding the provision of a patient safety card. Whilst the sponsor acknowledges that there may be differences in the characteristics of the current relapsed and/or refractory HL patient population and those patients post-ASCT at increased risk of relapse the sponsor does not believe these to be of sufficient magnitude to warrant a patient safety card for the HL consolidation patients. Regardless of whether a patient has relapsed and/or refractory HL or is at increased risk of HL relapse post-ASCT, both patient groups are likely to be under the principal supervision of a specialist haematologist overseeing their care. The sponsor believes that it is therefore unlikely that the post-ASCT at increased risk of HL relapse patients are likely to present at non-specialist centres as proposed by the Delegate. Furthermore, Adcetris is an IV administered product which must infused under the supervision of specialist healthcare professionals who are well versed in its benefit risk profile. Patients are typically treated as out-patients and must present every 3 weeks for treatment to infusion centres/hospitals for treatment. Unlike other jurisdictions, in Australia there is also a maximum limit of 16 cycles for Adcetris treatment, therefore the treatment duration is limited and well-defined. Collectively, the manner of prescribing, nature of administration, duration of disease and/or limitations on use help to ensure that post-ASCT patients at risk of HL relapse are not subjected to any additional risk than the currently approved patient population.

Although the sponsor does not believe a patient safety card is warranted, the sponsor does appreciate that there could be benefit to further enhancing the information contained within the PI and CMI with respect to highlighting the importance of physicians counselling patients and the need for vigilance. To this end the sponsor would be willing to supplement these documents through the addition of a 'Patient Counselling' section in the PI and more patient directed language in the CMI if the Delegate and ACPM deemed this appropriate.

Indication

The sponsor accepts the Delegate's proposed indication, although propose that the qualifier regarding PFS is more appropriate for inclusion in the 'Clinical Trials' section of the PI.[26]

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM) taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Adcetris vial for reconstitution and injection containing 50mg of brentuximab vedotin to have an overall positive benefit–risk profile for the Delegate's amended indication:

> *'Adcetris is indicated in the treatment of patients with CD30+ Hodgkin lymphoma at high risk of relapse or progression following ASCT.'*

[26] Arai S, Fanale M, Devos S, Engert A, Illidge T, Borchmann P, Younes A, Morschhauser F, McMillan A and Horning S (2013). Defining a Hodgkin Lymphoma Population for Novel Therapeutics after Relapse from Autologous Hematopoietic Cell Transplantation. Leukemia &Lymphoma 54:2531-3.
Chen R, et al. Five-Year Survival Data Demonstrating Durable Responses from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma. Poster. American Society of Hematology Annual Meeting. Orlando, FL; 2015. December 2015.
von Tresckow B, et al. Outcome and risk factors of patients with Hodgkin Lymphoma who relapse or progress after autologous stem cell transplant. Leukemia & Lymphoma (2014); 55: 1922-4.

In making this recommendation the ACPM:

- noted that this current submission moves treatment from those with established relapse (as per the currently approved indication), to those at risk of relapse following stem cell transplant.
- noted that the nature of the disease makes determination of the patient population at 'increased risk' difficult to ascertain.
- noted that brentuximab demonstrated efficacy by an increase in median duration of progression-free survival as compared to placebo. Treatment with brentuximab showed no effect on overall survival.
- noted that patients should be closely monitored for the serious hepatotoxicity during therapy, especially in patients with pre-existing hepatic impairment.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the PI about the monthly liver function tests
- PI could specify high and low risk based on the pivotal study to make it clear for prescribers.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Given the limitation of the patient population, does the committee consider there sufficient data to specify a degree of risk of relapse of disease progression which can be specified in the indication?*

Those with 'high risk' factors should be considered suitable for treatment, whereas those with 'low risk' factors are not considered eligible.

2. *Does the committee consider there to be a population of patients who should not receive consolidation brentuximab post-HSCT?*

The ACPM recommends that patients who do not have any high-risk features for progressive disease should not receive consolidation brentuximab treatment post-HSCT.

3. *What is the opinion of the committee regarding the provision of a patient safety card to those patients 'at risk' of relapse or disease progression?*

The ACPM agreed that a patient safety card is reasonable, especially for patients living in rural or remote areas.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Adcetris brentuximab vedotin vial for reconstitution and injection for the new indication of:

'*Adcetris is indicated in the treatment of patients with CD30+ Hodgkin lymphoma at higher risk of relapse or progression following ASCT (see 'Clinical Trials).*'

The full indications are now:

'Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (ASCT) or

2. 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 higher risk of relapse or progression following ASCT (see 'Clinical Trials').

Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).'

Specific conditions of registration applying to these goods

- Adcetris EU-RMP Version 5.2 (dated 23 February 2015, DLP 18 August 2014) and Australian Specific Annex (ASA) Version 5.0 (dated February 2016), and future updates where TGA approved will be implemented in Australia.

Attachment 1. Product Information

The PI for Adcetris approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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