

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

ADCETRIS 50 mg powder for concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of brentuximab vedotin.

After reconstitution (see section 6.6), each ml contains 5 mg of brentuximab vedotin.

ADCETRIS is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody (recombinant chimeric immunoglobulin G1 [IgG1], produced by recombinant DNA technology in Chinese Hamster ovary cells) that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE).

### Excipients with known effect

Each vial contains approximately 13.2 mg of sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white cake or powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADCETRIS is indicated for the 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.

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

## 4.2 Posology and method of administration

Brentuximab vedotin should be administered under the supervision of a physician experienced in the use of anti-cancer agents.

### Posology

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended starting dose for the retreatment of patients with relapsed or refractory HL or sALCL who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

#### *Renal impairment*

The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events (see section 5.2).

#### *Hepatic impairment*

The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events (see section 5.2).

If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see section 6.6).

Complete blood counts should be monitored prior to administration of each dose of this treatment (see section 4.4).

Patients should be monitored during and after infusion (see section 4.4).

Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Patients with relapsed or refractory HL or sALCL who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section 5.1).

For patients with HL at increased risk of relapse or progression following ASCT, ADCETRIS treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section 5.1).

Patients with CTCL should receive up to 16 cycles (see section 5.1).

### Dose adjustments

#### *Neutropenia*

If neutropenia develops during treatment it should be managed by dose delays. See Table 1 below for appropriate dosing recommendations (see also section 4.4).

Table 1: Dosing recommendations for neutropenia

| <b>Severity grade of neutropenia<br/>(signs and symptoms [abbreviated description of CTCAE<sup>a</sup>])</b>   | <b>Modification of dosing<br/>schedule</b>  |
|--|---|
| Grade 1 (<LLN - 1500/mm <sup>3</sup><br><LLN - 1.5 x 10 <sup>9</sup> /L) or<br>Grade 2 (<1500 - 1000/mm <sup>3</sup><br><1.5 - 1.0 x 10 <sup>9</sup> /L) | Continue with the same dose and schedule  |
| Grade 3 (<1,000 - 500/mm <sup>3</sup><br><1.0 - 0.5 x 10 <sup>9</sup> /L) or<br>Grade 4 (<500/mm <sup>3</sup><br><0.5 x 10 <sup>9</sup> /L)              | Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule <sup>b</sup> . Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia. |

<sup>a</sup>. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes; LLN= lower limit of normal

<sup>b</sup>. Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

#### *Peripheral neuropathy*

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 2 below for appropriate dosing recommendations (see section 4.4).

Table 2: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy

| <b>Severity of peripheral sensory or motor neuropathy<br/>(signs and symptoms [abbreviated description of CTCAE<sup>a</sup>])</b>       | <b>Modification of dose and<br/>schedule</b>   |
|---|--|
| Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)  | Continue with the same dose and schedule   |
| Grade 2 (interfering with function but not with activities of daily living) or<br>Grade 3 (interfering with activities of daily living) | Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks |
| Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)                      | Discontinue treatment  |

<sup>a</sup>. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

#### *Elderly*

Based upon population PK analyses (see section 5.2) and the safety profile in elderly patients, which are consistent with that of adult patients, the dosing recommendations for patients aged 65 and older are the same as for adults.

#### *Paediatric population*

The safety and efficacy of children less than 18 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

In nonclinical studies, thymus depletion has been observed (see section 5.3).

### Method of administration

The recommended dose of ADCETRIS is infused over 30 minutes.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Brentuximab vedotin must not be administered as an intravenous push or bolus. Brentuximab vedotin should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products (see section 6.2).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity.

### **4.4 Special warnings and precautions for use**

#### Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in brentuximab vedotin-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

#### Pancreatitis

Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported.

Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.

#### Pulmonary Toxicity

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g. cough, dyspnoea), a prompt diagnostic evaluation should be performed and

patients should be treated appropriately. Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement.

### Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, cytomegalovirus (CMV) (reactivation) and opportunistic infections such as *Pneumocystis jirovecii* pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

### Infusion-related reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

IRRs are more frequent and more severe in patients with antibodies to brentuximab vedotin (see section 4.8).

### Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with brentuximab vedotin. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

### Peripheral neuropathy

Brentuximab vedotin treatment may cause peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical trials, the majority of patients had improvement or resolution of their symptoms (see section 4.8). Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment (see section 4.2).

### Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged ( $\geq 1$  week) Grade 3 or Grade 4 neutropenia can occur with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, refer to section 4.2.

### Febrile neutropenia

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count  $< 1.0 \times 10^9/L$ , fever  $\geq 38.5^\circ C$ ; ref CTCAE v3) has been

reported with treatment with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

#### Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin. Fatal outcomes have been reported. If SJS or TEN occur, treatment with brentuximab vedotin should be discontinued and appropriate medical therapy should be administered.

#### Gastrointestinal Complications

Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

#### Hepatotoxicity

Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with brentuximab vedotin. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Liver function should be tested before initiating the treatment and routinely monitored in patients receiving brentuximab vedotin. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of brentuximab vedotin.

#### Hyperglycaemia

Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

#### Renal and hepatic impairment

There is limited experience in patients with renal and hepatic impairment. Available data indicate that MMAE clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations (see section 5.2).

#### CD30+ CTCL

The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. In two single arm phase II studies of brentuximab vedotin, disease activity has been shown in the subtypes Sézary syndrome (SS), lymphomatoid papulosis (LyP) and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, ADCETRIS should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis (see section 5.1).

#### Sodium content in excipients

This medicinal product contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. To be taken into consideration for patients on a controlled sodium diet.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Interaction with medicinal products metabolized through CYP3A4 route (CYP3A4 inhibitors/inducers)

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 1: Dosing recommendations for neutropenia (see section 4.2).

Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin. Though PK data are limited, co administration of rifampicin appeared to reduce plasma concentrations of MMAE metabolites that could be assayed.

Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

#### **4.6 Fertility, pregnancy and lactation**

##### Women of childbearing potential

Women of childbearing potential should be using two methods of effective contraception during treatment with brentuximab vedotin and until 6 months after treatment.

##### Pregnancy

There are no data from the use of brentuximab vedotin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Brentuximab vedotin should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus.

See the fertility section below pertaining to advice for women whose male partners are being treated with brentuximab vedotin.

##### Breastfeeding

There are no data as to whether brentuximab vedotin or its metabolites are excreted in human milk.

A risk to the newborn/infant cannot be excluded.

A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy, taking into account a potential risk of breast-feeding for the child and the benefit of therapy for the woman.

##### Fertility

In non-clinical studies, brentuximab vedotin treatment has resulted in testicular toxicity, and may alter male fertility. MMAE has been shown to have aneugenic properties (see section 5.3). Therefore, men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.



#### 4.7 Effects on ability to drive and use machines

Brentuximab vedotin may have a minor influence on the ability to drive and use machines.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below and in Table 3 have been determined based on data generated from clinical studies.

In the pooled dataset of ADCETRIS as monotherapy across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) the most frequent adverse reactions ( $\geq 10\%$ ) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain.

Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was  $\leq 1\%$ .

Adverse events led to treatment discontinuation in 24% of patients receiving brentuximab vedotin.

The safety data in patients retreated with ADCETRIS (SGN35-006, see section 5.1) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data in patients with relapsed or refractory HL who had not received an autologous stem cell transplant and were treated with the recommended dose of 1.8 mg/kg every three weeks in a single-arm phase 4 study (n=60), the phase 1 dose escalation and clinical pharmacology studies (n=15 patients) and in the NPP (n=26 patients) (see section 5.1) were consistent with the safety profile of the pivotal clinical studies.

##### Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 3). Within each System Organ Class, adverse reactions are listed under frequency categories of: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

Table 3: Adverse reactions to ADCETRIS

| System organ class  | Adverse reactions   |
|---|---|
| <b>Infections and infestations</b>                          |   |
| Very common:  | Infection <sup>a</sup> , upper respiratory tract infection  |
| Common:   | Herpes zoster, pneumonia, herpes simplex, oral candidiasis  |
| Uncommon:   | Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock |
| Frequency not known:  | Progressive multifocal leukoencephalopathy  |
| <b>Blood and lymphatic system disorders</b>                 |   |
| Very common:  | Neutropenia   |
| Common:   | Anaemia, thrombocytopenia   |
| Uncommon:   | Febrile neutropenia   |
| <b>Immune system disorders</b>                              |   |
| Uncommon:   | Anaphylactic reaction   |
| <b>Metabolism and nutrition disorders</b>                   |   |
| Common:   | Hyperglycaemia  |
| Uncommon:   | Tumour lysis syndrome   |
| <b>Nervous system disorders</b>                             |   |
| Very common:  | Peripheral sensory neuropathy, peripheral motor neuropathy  |
| Common:   | Dizziness   |
| Uncommon:   | Demyelinating polyneuropathy  |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |   |
| Very Common:  | Cough, dyspnoea   |
| <b>Gastro-intestinal disorders</b>                          |   |
| Very common:  | Nausea, diarrhoea vomiting, constipation, abdominal pain  |
| Uncommon:   | Pancreatitis acute  |
| <b>Hepatobiliary disorders</b>                              |   |
| Common:   | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased   |
| <b>Skin and subcutaneous tissue disorders</b>               |   |
| Very common:  | Rash <sup>a</sup> , pruritus  |
| Common:   | Alopecia  |
| Uncommon:   | Stevens-Johnson syndrome/toxic epidermal necrolysis   |
| <b>Musculoskeletal and connective tissue disorders</b>      |   |
| Very common:  | Arthralgia, myalgia   |
| Common:   | Back pain   |
| <b>General disorders and administration site conditions</b> |   |
| Very common:  | Fatigue, pyrexia, infusion-related reactions <sup>a</sup>   |
| Common:   | Chills  |
| <b>Investigations</b>                                       |   |
| Very common:  | Weight decreased  |

<sup>a</sup> Represents pooling of preferred terms.

#### Description of selected adverse reactions

##### *Neutropenia*

In clinical trials, neutropenia led to dose delays in 14% of patients. Grade 3 neutropenia was reported in 13% and Grade 4 neutropenia was reported in 5% of patients. No patients required dose reduction or discontinued treatment for neutropenia.

Severe and prolonged ( $\geq 1$  week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. Febrile neutropenia reported in  $< 1\%$  of the patients (see section 4.2).

In the pivotal phase 2 population (SG035-0003 and SG035-0004), the median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted  $\geq 7$  days. Less than half of the patients in the pivotal phase 2 population with Grade 3 or Grade 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or Grade 2.

#### *Serious infections and opportunistic infections*

In clinical trials, serious infections and opportunistic infections occurred in 10% of patients, sepsis or septic shock occurred in  $< 1\%$  of the patients. The most commonly reported opportunistic infections were herpes zoster and herpes simplex.

#### *Peripheral neuropathy*

In clinical trials treatment emergent neuropathy occurred in 59% of the population, peripheral motor neuropathy occurred in 14% of patients. Peripheral neuropathy led to treatment discontinuation in 15%, dose reductions in 15%, and dose delays in 17% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 12 weeks. The median duration of treatment for patients who discontinued due to peripheral neuropathy was 12 cycles.

Among patients who experienced peripheral neuropathy in the pivotal phase 2 studies (SG035-0003 and SG035-0004) and randomized phase 3 studies (SGN35-005 and C25001), the median follow up time from end of treatment until last evaluation ranged from 48.9 to 98 weeks. At the time of last evaluation, most of the patients (82-85%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement for all events ranged from 16 to 23.4 weeks.

In patients with relapsed or refractory HL or sALCL who were retreated with brentuximab vedotin (SGN35-006), the majority of patients (80%) also had improvement or resolution of their peripheral neuropathy symptoms at the time of last evaluation.

#### *Infusion-related reactions*

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough were reported in 13% of patients. Anaphylactic reactions have been reported (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

#### *Immunogenicity*

In clinical trials, patients were periodically tested for antibodies to brentuximab vedotin using a sensitive electrochemiluminescent immunoassay. There was a higher incidence of infusion-related reactions observed in patients with antibodies to brentuximab vedotin relative to patients who tested transiently positive or negative.

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. While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive anti-drug antibodies (ADA) relative to patients with transiently positive ADA and never positive ADA. There was a trend of increased clearance of brentuximab vedotin in paediatric

patients confirmed positive for ADAs. No patients aged <12 years (0 of 11) and 2 patients aged ≥12 years (2 of 23) became persistently ADA positive.

#### Paediatric population

Safety was evaluated in a phase 1/2 study in paediatric patients aged 7-17 years of age (n=36) with relapsed or refractory (r/r) HL and sALCL (see section 5.1). In this study in 36 patients, no new safety concerns were reported.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### **4.9 Overdose**

There is no known antidote for overdose of brentuximab vedotin. In case of overdose, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered (see section 4.4).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents; monoclonal antibodies, ATC code: L01XC12

#### Mechanism of action

Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

Classical HL, sALCL and subtypes of CTCL (including MF and pcALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL, sALCL and CD30+ CTCL disease and therapeutic spectrums and clinical evidence in CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL, sALCL with or without prior ASCT and CD30+ CTCL after at least 1 prior systemic therapy.

Contributions to the mechanism of action by other antibody associated functions have not been excluded.

## Pharmacodynamic effects

### *Cardiac electrophysiology*

Forty-six (46) patients with CD30-expressing hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The primary objective was to evaluate the effect of brentuximab vedotin on cardiac ventricular re-polarization and the predefined primary analysis was the change in QTc from baseline to multiple time points in Cycle 1.

The upper 90% confidence interval (CI) around the mean effect on QTc was <10 msec at each of the Cycle 1 and Cycle 3 post-baseline time points. These data indicate the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30-expressing malignancies.

## Clinical efficacy

### *Hodgkin lymphoma*

#### Study SG035-0003

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in a pivotal open-label, single-arm, multicenter study in 102 patients with relapsed or refractory HL. See Table 4 below for a summary of baseline patient and disease characteristics.

Table 4: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory HL study

| <b>Patient characteristics</b>                       | <b>N = 102</b>      |
|--|---------------------|
| Median age, yrs (range)                              | 31 years (15-77)    |
| Gender   | 48M (47%)/54F (53%) |
| ECOG status  |                     |
| 0  | 42 (41%)            |
| 1  | 60 (59%)            |
| Prior ASCT   | 102 (100%)          |
| Prior chemotherapy Regimens                          | 3.5 (1-13)          |
| Time from ASCT to first post-transplant relapse      | 6.7 mo (0-131)      |
| Histologically confirmed CD30-expressing disease     | 102 (100%)          |
| <b>Disease characteristics</b>                       |                     |
| Primary Refractory to frontline therapy <sup>a</sup> | 72 (71%)            |
| Refractory to most recent therapy                    | 43 (42%)            |
| Baseline B symptoms                                  | 35 (33%)            |
| Stage III at initial diagnosis                       | 27 (26%)            |
| Stage IV at initial diagnosis                        | 20 (20%)            |

<sup>a</sup> Primary refractory HL is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

Eighteen (18) patients (18%) received 16 cycles of brentuximab vedotin; and the median number of cycles received was 9 (ranging from 1 to 16).

Response to treatment with brentuximab vedotin was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13, and 16 with PET at cycles 4 and 7.

The objective response rate (ORR) per IRF assessment was 75% (76 of 102 patients in the intent-to-treat [ITT] set) and tumour reduction was achieved in 94% of patients. Complete remission (CR) was 33% (34 of 102 patients in the ITT set). The median overall survival (OS) is 40.5 months (the median

observation time (time to death or last contact) from first dose was 35.1 months (range 1.8 to 72.9+ months). The estimated overall survival rate at 5 years was 41% (95% CI [31%, 51%]). The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 8 responding patients went on to receive an allogeneic SCT. For further efficacy results see Table 5.

Table 5: Efficacy results in relapsed or refractory Hodgkin lymphoma patients treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks

| <b>Best clinical response (N = 102)</b>        | <b>IRF N (%)</b>      | <b>95% CI</b>         |
|--|-----------------------|-----------------------|
| Objective response rate (CR + PR)              | 76 (75)               | 64.9, 82.6            |
| Complete remission (CR)                        | 34 (33)               | 24.3, 43.4            |
| Partial remission (PR)                         | 42 (41)               | NA                    |
| Disease control rate (CR + PR + SD)            | 98 (96)               | 90.3, 98.9            |
| <b>Duration of response</b>                    | <b>Median per IRF</b> | <b>95% CI</b>         |
| Objective response rate (CR + PR) <sup>a</sup> | 6.7 months            | 3.6, 14.8             |
| Complete remission (CR)                        | 27.9 months           | 10.8, NE <sup>b</sup> |
| <b>Overall survival</b>                        |                       | <b>95% CI</b>         |
| Median   | 40.5 months           | 28.7, 61.9            |
| Estimated 5-year OS Rate                       | 41%                   | 31%, 51%              |

<sup>a</sup>. The range of DOR was 1.2+ months to 43+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 9.0 months.

<sup>b</sup>. Not estimable.

An exploratory intra-patient analysis showed that approximately 64% of the HL patients treated with brentuximab vedotin as part of the SG035-0003 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Of the 35 patients (33%) who had B symptoms at baseline, 27 patients (77%) experienced resolution of all B symptoms at a median time of 0.7 months from initiation of brentuximab vedotin.

#### Data in HL Patients Who Are Not Stem Cell Transplant (SCT) Candidates

##### Study C25007

A phase 4 single-arm study was conducted in patients with relapsed or refractory HL (n=60) who had received at least one prior chemotherapeutic regimen and at the time of treatment initiation with brentuximab vedotin were not considered candidates for SCT or multiagent chemotherapy. The median number of cycles was 7 (range 1 to 16 cycles). Patients were treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks. Per IRF, the objective response rate (ORR) in the ITT population was 50% (95% CI, 37; 63%). A best overall response of CR was reported for 7 patients (12%); PR was reported for 23 patients (38%). Among these 30 patients, the median time to response, defined as the time from first dose to the soonest of PR or CR, was 6 weeks (range, 5 to 39 weeks). The median time to best overall response, defined as the time from first dose to the clinical best response of CR or PR, was 11 weeks (range, 5 to 60 weeks). Twenty-eight patients (47%) went on to receive SCT after a median of 7 cycles (range, 4 to 16 cycles) of brentuximab vedotin treatment. The 32 patients (53%) who did not receive subsequent SCT also received brentuximab vedotin for a median of 7 cycles (range, 1 to 16 cycles).

Of the study's 60 patients, 49 patients (82%) received >1 prior cancer-related treatment and 11 patients (18%) received 1 prior cancer-related treatment. Per IRF, the ORR was 51% (95% CI [36%, 66%]) for the patients who had received >1 prior cancer-related treatment and 45% (95% CI [17%, 77%]) for the patients who had received 1 prior cancer-related treatment. For the patients who received >1 prior cancer-related treatment, a best overall response of CR was reported for 6 patients (12%); PR was reported for 19 patients (39%). For the patients who received 1 prior cancer-related treatment, CR was reported for 1 patient (9%) and PR was reported for 4 patients (36%). Out of the

49 patients receiving >1 line of prior treatment, 22 patients (45%) received subsequent SCT; of the 11 patients who had received 1 prior treatment, 6 patients (55%) received subsequent SCT.

Data were also collected from patients (n=15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n=26) in a NPP, with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks.

Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with brentuximab vedotin. Fifty nine percent (59%) of patients had advanced stage disease (stage III or IV) at initial diagnosis.

Results from these phase 1 studies and from the NPP experience showed, that in patients with relapsed or refractory HL without prior ASCT, clinically meaningful responses can be achieved as evidenced by an investigator-assessed, objective response rate of 54% and a complete remission rate of 22% after a median of 5 cycles of brentuximab vedotin.

#### Study SGN35-005

The efficacy and safety of brentuximab vedotin were evaluated in a randomized, double-blind, placebo-controlled, 2-arm multicenter trial in 329 patients with HL at risk of relapse or progression following ASCT. Patients with known cerebral/meningeal disease, including history of PML were excluded from the study. See Table 6 for patient characteristics. Of the 329 patients, 165 patients were randomized to the treatment arm and 164 patients were randomized to the placebo arm. In the study, patients were to receive their first dose after recovery from ASCT (between days 30-45 following ASCT). Patients were treated with 1.8 mg/kg of ADCETRIS or matching placebo intravenously over 30 minutes every 3 weeks for up to 16 cycles.

Eligible patients were required to have at least one of the following risk factors:

- HL that was refractory to frontline treatment
- Relapsed or progressive HL that occurred <12 months from the end of frontline treatment
- Extranodal involvement at time of pre-ASCT relapse, including extranodal extension of nodal masses into adjacent vital organs

Table 6: Summary of Baseline Patient and Disease Characteristics in the Phase 3 HL post-ASCT Study

| <b>Patient characteristics</b>  | <b>Brentuximab vedotin<br/>N = 165</b> | <b>Placebo<br/>N = 164</b> |
|---|--|----------------------------|
| Median age, yrs (range)   | 33 years (18-71)                       | 32 years (18-76)           |
| Gender  | 76M (46%)/89F (54%)                    | 97M (59%)/67F (41%)        |
| ECOG status   |  |                            |
| 0   | 87 (53%)                               | 97 (59%)                   |
| 1   | 77 (47%)                               | 67 (41%)                   |
| 2   | 1 (1%)                                 | 0                          |
| <b>Disease characteristics</b>  |  |                            |
| Median number of prior chemotherapy regimens (range)                    | 2 (2-8)                                | 2 (2-7)                    |
| Median time from HL diagnosis to first dose (range)                     | 18.7 mo (6.1-204.0)                    | 18.8 mo (7.4-180.8)        |
| Disease stage at initial diagnosis of HL                                |  |                            |
| Stage I   | 1 (1%)                                 | 5 (3%)                     |
| Stage II  | 73 (44%)                               | 61 (37%)                   |
| Stage III   | 48 (29%)                               | 45 (27%)                   |
| Stage IV  | 43 (26%)                               | 51 (31%)                   |
| Unknown   | 0                                      | 2 (1%)                     |
| PET scan Status prior to ASCT   |  |                            |
| FDG-AVID  | 64 (39%)                               | 51 (31%)                   |
| FDG-NEGATIVE  | 56 (34%)                               | 57 (35%)                   |
| NOT DONE  | 45 (27%)                               | 56 (34%)                   |
| Extranodal involvement at time of pre-ASCT relapse                      | 54 (33%)                               | 53 (32%)                   |
| B symptoms <sup>a</sup>   | 47 (28%)                               | 40 (24%)                   |
| Best response to salvage therapy pre-ASCT <sup>b</sup>                  |  |                            |
| Complete Response   | 61 (37%)                               | 62 (38%)                   |
| Partial Response  | 57 (35%)                               | 56 (34%)                   |
| Stable Response   | 47 (28%)                               | 46 (28%)                   |
| HL Status after the end of frontline standard chemotherapy <sup>b</sup> |  |                            |
| Refractory  | 99 (60%)                               | 97 (59%)                   |
| Refractory occurred <12 months  | 53 (32%)                               | 54 (33%)                   |
| Relapse occurred >=12 months  | 13 (8%)                                | 13 (8%)                    |

<sup>a</sup>. For refractory disease, or upon progression or relapse after frontline therapy.

<sup>b</sup>. Stratification factors at randomization.



The efficacy results are shown in Table 7. The primary endpoint of PFS was met and showed a difference in median PFS of 18.8 months in favour of the treatment arm.

Table 7: Efficacy Results in HL Patients at Increased Risk of Relapse or Progression Following ASCT Treated with 1.8 mg/kg of Brentuximab Vedotin Every 3 Weeks

|  | <b>Brentuximab Vedotin</b><br>N = 165 | <b>Placebo</b><br>N = 164         | <b>Stratified Hazard Ratio</b>                                       |
|--|---------------------------------------|-----------------------------------|--|
| <b>Progression Free Survival<sup>a</sup></b> | <b>Median per IRF</b>                 |                                   |  |
|  | 42.9 months<br>(95% CI [30.4, 42.9])  | 24.1 months<br>(95% CI [11.5, -]) | 0.57<br>(95% CI [0.40, 0.81])<br>Stratified log-rank test<br>P=0.001 |
|  | <b>Median per Investigator</b>        |                                   |  |
|  | Not Reached<br>(95% CI [26.4, -])     | 15.8 months<br>(95% CI [8.5, -])  | 0.5<br>(95% CI [0.36, 0.70]) <sup>b</sup>                            |
| <b>Overall Survival</b>                      | <b>Number of Deaths (%)</b>           |                                   |  |
|  | 28 (17)                               | 25 (15)                           | 1.15<br>(95% CI [0.67, 1.97])  |

<sup>a</sup>. At the time of the primary analysis, the median follow-up time for both arms was 30 months [range, 0 to 50].

<sup>b</sup>. Stratified log-rank test was not performed for PFS per Investigator.

Pre-specified subgroup analyses of PFS per IRF were performed by patients' best response to pre-ASCT salvage therapy, HL status after frontline therapy, age, gender, baseline weight, baseline ECOG performance status, number of treatments pre-ASCT, geographic region, pre-ASCT PET status, B symptom status after failure of frontline therapy, and pre-ASCT extranodal disease status. The analyses showed a consistent trend towards benefit for patients who received brentuximab vedotin compared with patients who received placebo with the exception of patients  $\geq 65$  years of age (n=8).

No differences were observed in quality of life between the treatment and placebo arms. Medical resource utilization (MRU) analysis showed that hospitalizations and outpatient visits, as well as working days/other activities missed by patients and caregivers were lower with brentuximab vedotin compared with placebo in patients with HL at increased risk of relapse.

An updated analysis conducted after 3 years of follow-up showed a sustained PFS improvement per IRF (HR = 0.58 [95% CI (0.41, 0.81)]).

#### Post-hoc Risk Factor Analyses

Post-hoc analyses were performed to evaluate the impact of increased risk (number of risk factors) on clinical benefit (Table 8). Representative risk factors for these analyses were:

- HL that occurred <12 months or HL that was refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy as determined by CT and/or PET scanning

- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- Two or more prior salvage therapies.

The results of these post-hoc analyses suggest increased clinical benefit for patients with two or more risk factors but no difference based on any of the individual risk factors. No benefit in terms of PFS or OS has been observed in patients with one risk factor for relapse or progression.

Table 8: Summary of PFS per IRF and OS by Number of Risk Factors in the Phase 3 HL post-ASCT Study

| <b>Progression Free Survival per IRF</b>                              |   |                           |  |                            |                                       |                           |
|---|---|---------------------------|--|----------------------------|---------------------------------------|---------------------------|
|   | <b>Number of Risk Factors = 1</b>           |                           | <b>Number of Risk Factors ≥ 2</b>      |                            | <b>Number of Risk Factors ≥ 3</b>     |                           |
|   | <b>Brentuximab Vedotin<br/>N = 21</b>       | <b>Placebo<br/>N = 28</b> | <b>Brentuximab Vedotin<br/>N = 144</b> | <b>Placebo<br/>N = 136</b> | <b>Brentuximab Vedotin<br/>N = 82</b> | <b>Placebo<br/>N = 84</b> |
| Number of patients with disease progression or death <sup>a</sup> (%) | 9 (43)                                      | 7 (25)                    | 51 (35)                                | 68 (50)                    | 32 (39)                               | 49 (58)                   |
| Stratified Hazard Ratio   | 1.65<br>(95% CI [0.60, 4.55]) <sup>b</sup>  |                           | 0.49<br>(95% CI [0.34, 0.71])          |                            | 0.43<br>(95% CI [0.27, 0.68])         |                           |
| <b>Overall Survival</b>   |   |                           |  |                            |                                       |                           |
|   | <b>Number of Risk Factors = 1</b>           |                           | <b>Number of Risk Factors ≥ 2</b>      |                            | <b>Number of Risk Factors ≥ 3</b>     |                           |
|   | <b>Brentuximab Vedotin<br/>N = 21</b>       | <b>Placebo<br/>N = 28</b> | <b>Brentuximab Vedotin<br/>N = 144</b> | <b>Placebo<br/>N = 136</b> | <b>Brentuximab Vedotin<br/>N = 82</b> | <b>Placebo<br/>N = 84</b> |
| Number of deaths <sup>c</sup> (%)                                     | 5 (24)                                      | 1 (4)                     | 23 (16)                                | 24 (18)                    | 15 (18)                               | 16 (19)                   |
| Stratified Hazard Ratio   | 7.94<br>(95% CI [0.93, 68.06]) <sup>b</sup> |                           | 0.94<br>(95% CI [0.53, 1.67])          |                            | 0.92<br>(95% CI [0.45, 1.88])         |                           |

<sup>a</sup> Death without either prior progression or more than one missed assessment visit.

<sup>b</sup> Indicates results from non-stratified analysis.

<sup>c</sup> Events are death due to any cause.

At the time of the updated analysis (3 years of follow-up) for patients with 2 or more risk factors, the hazard ratio for PFS per IRF was 0.49 (95% CI [0.34, 0.71]) and the hazard ratio for PFS per investigator was 0.41 (95% CI [0.29, 0.58]) (see Figures 1 and 2).

Figure 1: Kaplan-Meier Plot of PFS per IRF in Patients with  $\geq 2$  Risk Factors

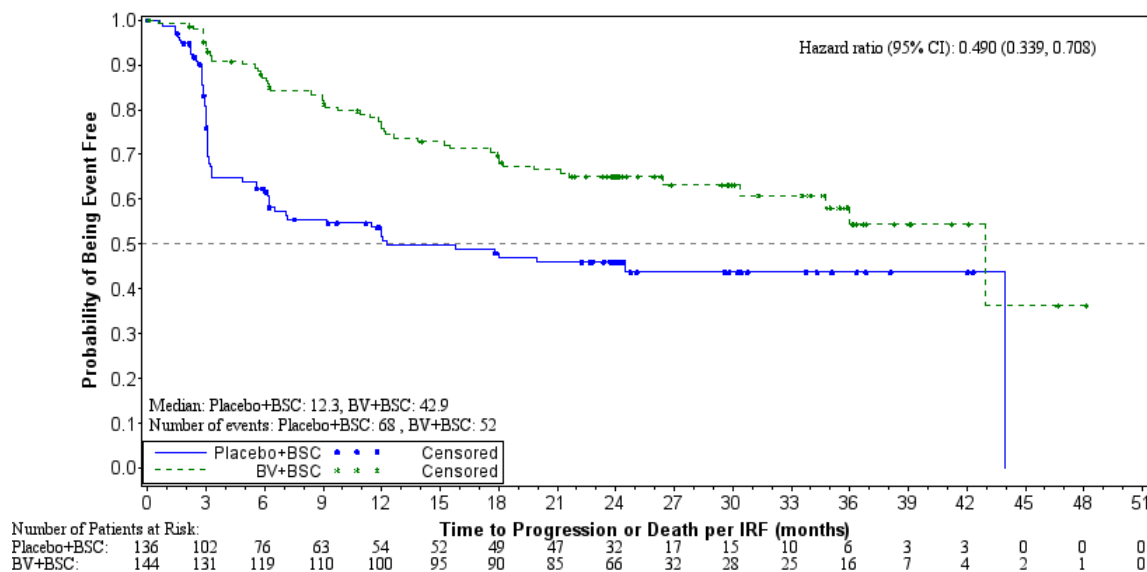
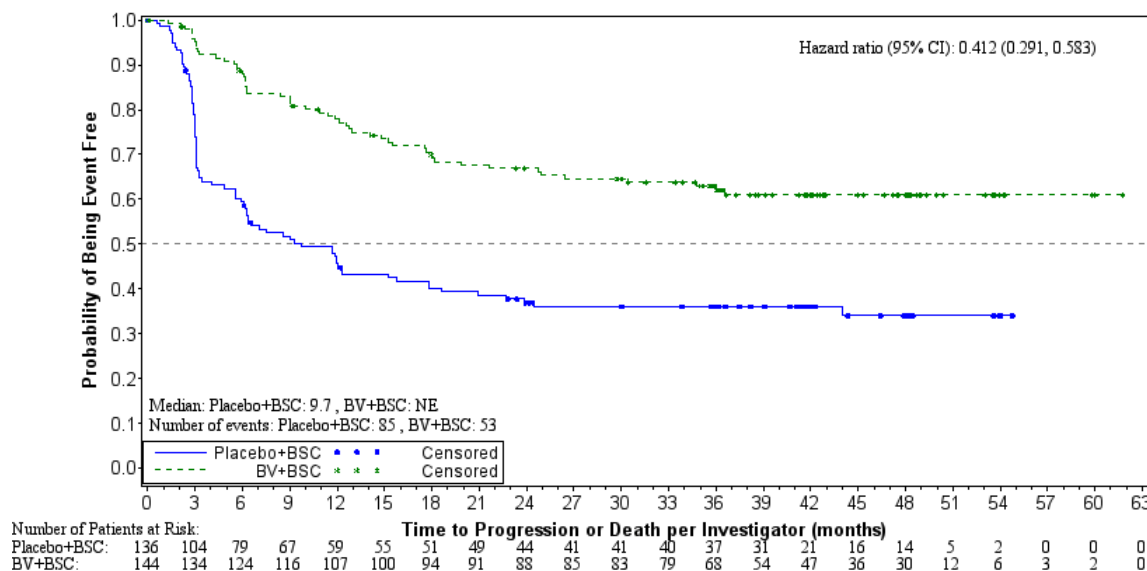


Figure 2: Kaplan-Meier Plot of PFS per Investigator in Patients with  $\geq 2$  Risk Factors



### Study SGN35-006 (Retreatment Study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin was evaluated in a phase 2, open-label, multicenter trial. Twenty patients with relapsed or refractory HL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 7 (range, 2 to 37 cycles). Of the 20 evaluable patients with HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with brentuximab vedotin retreatment, for an ORR of 60%. The median duration of response was 9.2 and 9.4 months in patients who achieved OR (CR+PR) and CR, respectively.

### Systemic anaplastic large cell lymphoma

#### Study SG035-0004

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in an open-label, single-arm, multicenter study in 58 patients with relapsed or refractory sALCL. See Table 9 below for a summary of baseline patient and disease characteristics.

Table 9: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study

| <b>Patient characteristics</b>                       | <b>N = 58</b>       |
|--|---------------------|
| Median age, yrs (range)                              | 52 years (14-76)    |
| Gender   | 33M (57%)/25F (43%) |
| ECOG status <sup>a</sup>                             |                     |
| 0  | 19 (33%)            |
| 1  | 38 (66%)            |
| Prior ASCT   | 15 (26%)            |
| Prior chemotherapy Regimens (range)                  | 2 (1-6)             |
| Histologically confirmed CD30-expressing disease     | 57 (98%)            |
| Anaplastic lymphoma kinase (ALK)-negative disease    | 42 (72%)            |
| <b>Disease characteristics</b>                       |                     |
| Primary Refractory to frontline therapy <sup>b</sup> | 36 (62%)            |
| Refractory to most recent therapy                    | 29 (50%)            |
| Relapsed to most recent therapy                      | 29 (50%)            |
| Baseline B symptoms                                  | 17 (29%)            |
| Stage III at initial diagnosis                       | 8 (14%)             |
| Stage IV at initial diagnosis                        | 21 (36%)            |

- a. One patient had a baseline ECOG status of 2, which was prohibited by protocol and is captured as Inclusion Criteria Not Met.
- b. Primary refractory sALCL is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

The median time from initial sALCL diagnosis to first dose with brentuximab vedotin was 16.8 months.

Ten (10) patients (17%) received 16 cycles of brentuximab vedotin; the median number of cycles received was 7 (range, 1 to 16).

Response to treatment with brentuximab vedotin was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13 and 16 with PET at cycles 4 and 7.

The ORR per IRF assessment was 86% (50 of 58 patients in the ITT set). CR was 59% (34 of 58 patients in the ITT set) and tumour reduction (of any degree) was achieved in 97% of patients. The estimated overall survival at 5 years was 60% (95% CI [47%,73%]). The median observation time (time to death or last contact) from first dose was 71.4 months. The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 9 responding patients went on to receive an allogeneic stem cell transplant (SCT) and 9 responding patients went on to autologous SCT. For further efficacy results, see Table 10 and Figure 3.

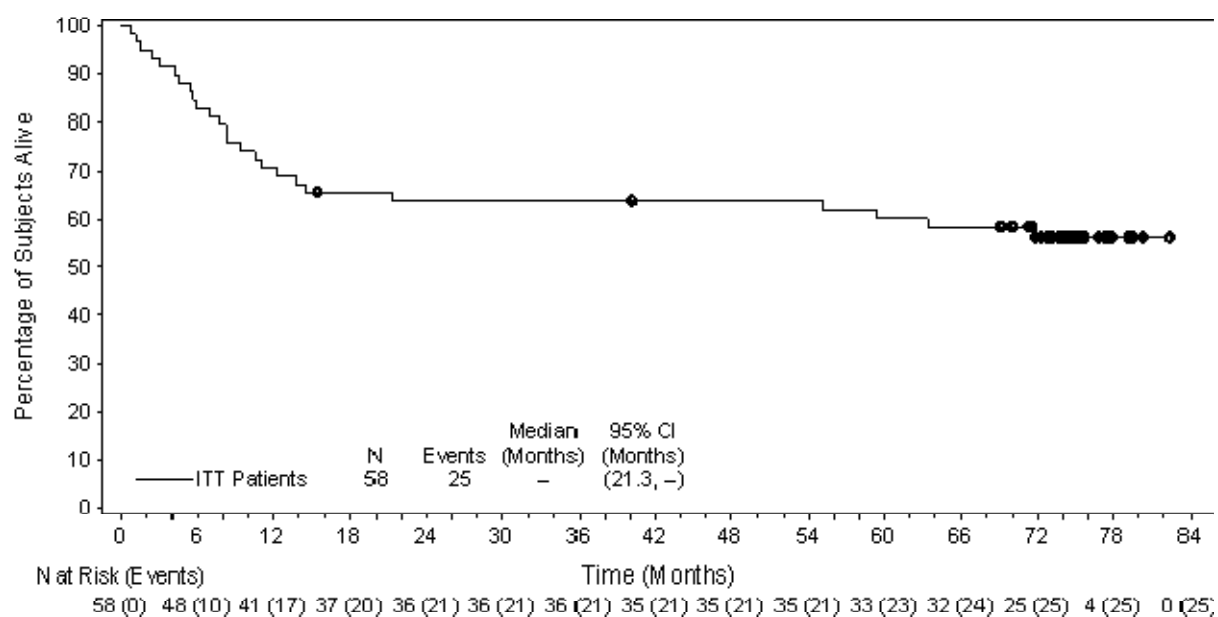
Table 10: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks

| <b>Best clinical response (N = 58)</b>    | <b>IRF N (%)</b>      | <b>95% CI</b>         |
|---|-----------------------|-----------------------|
| Objective response rate (CR + PR)         | 50 (86)               | 74.6, 93.9            |
| Complete remission (CR)                   | 34 (59)               | 44.9, 71.4            |
| Partial remission (PR)                    | 16 (28)               | NA                    |
| Disease control rate (CR + PR + SD)       | 52 (90)               | 78.8, 96.1            |
| <b>Duration of response</b>               | <b>Median per IRF</b> | <b>95% CI</b>         |
| Objective response (CR + PR) <sup>a</sup> | 13.2                  | 5.7, 26.3             |
| Complete remission (CR)                   | 26.3                  | 13.2, NE <sup>b</sup> |
| <b>Progression Free Survival</b>          | <b>Median per IRF</b> | <b>95% CI</b>         |
| Median                                    | 14.6                  | 6.9, 20.6             |
| <b>Overall survival</b>                   | <b>Median</b>         | <b>95% CI</b>         |
| Median                                    | Not reached           | 21.3, NE <sup>b</sup> |

<sup>a</sup>. The range of DOR was 0.1 months to 39.1+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 15.5 months.

<sup>b</sup>. Not estimable.

Figure 3: Kaplan-Meier Plot of OS



An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with brentuximab vedotin as part of the SG035-0004 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Of the 17 patients (29%) who had B symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms in a median time from initiation of brentuximab vedotin of 0.7 months.

#### Study SGN35-006 (Retreatment study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin was evaluated in a phase 2, open-label, multicenter trial. Seven patients with relapsed sALCL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 8.5 (range, 2 to 30 cycles). Of the 8 sALCL patients, 3 were retreated twice for a total of 11 retreatment experiences. Retreatments with brentuximab vedotin resulted in 6 CRs (55%)

and 4 PRs (36%), for an ORR of 91%. The median duration of response was 8.8 and 12.3 months in patients who achieved OR (CR+PR) and CR, respectively.

### *Cutaneous T-cell lymphoma*

#### Study C25001

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in a pivotal phase 3, open-label, randomised, multicentre study in 128 patients with histologically confirmed CD30+ CTCL. CD30 positivity was defined as  $\geq 10\%$  target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern based on an immunohistochemistry assay (Ventana anti-CD30 [Ber-H2]). Patients with a diagnosis of mycosis fungoides [MF] or primary cutaneous anaplastic large cell lymphoma [pcALCL] were considered eligible for the study. Patients were stratified by these disease types and randomised 1:1 to receive either brentuximab vedotin or the physician's choice of either methotrexate or bexarotene. Patients with pcALCL received either prior radiation therapy or at least 1 prior systemic therapy and patients with MF received at least 1 prior systemic therapy. Patients with a concurrent diagnosis of systemic ALCL, Sezary syndrome and other non-Hodgkin lymphoma (except for lymphomatoid papulosis [LyP]) were excluded from this study. Patients were treated with 1.8 mg/kg of brentuximab vedotin intravenously over 30 minutes every 3 weeks for up to 16 cycles or physician's choice for up to 48 weeks. The median number of cycles was approximately 12 cycles in the brentuximab vedotin arm. In the physician's choice arm, the median duration of treatment (number of cycles) for patients receiving bexarotene was approximately 16 weeks (5.5 cycles) and 11 weeks (3 cycles) for patients receiving methotrexate. Table 11 provides a summary of the baseline patient and disease characteristics.

Table 11: Summary of Baseline Patient and Disease Characteristics in the Phase 3 CTCL Study (ITT Population)

| <b>Patient characteristics</b>                   | <b>Brentuximab vedotin<br/>N = 64</b> | <b>Physician's Choice<br/>(Methotrexate or<br/>Bexarotene)<br/>N= 64</b> |
|--|---------------------------------------|--|
| Median age (range)                               | 62 years (22-83)                      | 58.5 years (22-83)   |
| Patients $\geq 65$ years old n (%)               | 28 (44%)                              | 24 (38%)   |
| Gender n (%)                                     | 33M (52%)/31F (48%)                   | 37M (58%)/27F (42%)  |
| ECOG status n (%)                                |                                       |  |
| 0  | 43 (67)                               | 46 (72)  |
| 1  | 18 (28)                               | 16 (25)  |
| 2  | 3 (5)                                 | 2 (3)  |
| <b>Disease characteristics</b>                   |                                       |  |
| Median number of prior therapies (range)         | 4 (0-13)                              | 3.5 (1-15)   |
| Median number of skin-directed therapies (range) | 1 (0-6)                               | 1 (0-9)  |
| Median number of systemic therapies (range)      | 2 (0-11)                              | 2 (1-8)  |
| MF, n (%)  | 48 (75)                               | 49 (77)  |
| Early (IA-IIA)                                   | 15 (31)                               | 18 (37)  |
| Advanced (IIB-IVB <sup>a</sup> )                 | 32 (67)                               | 30 (61)  |
| pcALCL, n (%)                                    | 16 (25)                               | 15 (23)  |
| Skin only  | 9 (56)                                | 11 (73)  |
| Extracutaneous disease                           | 7 (44)                                | 4 (27)   |

<sup>a</sup> One patient in each arm had incomplete staging data and are not included in the table

The most common prior skin directed therapies in the ITT population were radiotherapy (64%), phototherapy (48%) and topical steroids (17%). The most common prior systemic therapies in the ITT population were chemotherapy (71%), immunotherapy (43%) and bexarotene (38%).

The primary endpoint was objective response rate that lasts at least 4 months (ORR4) (duration from first response to last response  $\geq$  4 months), as determined by an independent review of the Global Response Score (GRS) consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] as assessed per investigator), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (Olsen 2011). Table 12 includes the results for ORR4 and other key secondary endpoints.

Table 12: Efficacy Results in CTCL Patients Treated with 1.8 mg/kg of Brentuximab Vedotin Every 3 Weeks (ITT Population)

|   | <b>Brentuximab vedotin<br/>N=64</b> | <b>Physician's Choice<br/>(Methotrexate or Bexarotene)<br/>N=64</b> |
|---|-------------------------------------|---|
| <b>Objective Response Rate lasting at least 4 months (ORR4) per IRF</b> |                                     |   |
| N (%)   | 36 (56.3)                           | 8 (12.5)  |
| Percent Difference (95% CI)   |                                     | 43.8 (29.1, 58.4)   |
| p-value   |                                     | <0.001  |
| <b>Complete Response (CR) per IRF</b>                                   |                                     |   |
| N (%)   | 10 (15.6)                           | 1 (1.6)   |
| Percent Difference (95% CI)   |                                     | 14.1 (-4.0, 31.5)   |
| Adjusted p-value <sup>a</sup>   |                                     | 0.0046  |
| <b>Progression Free Survival (PFS) per IRF</b>                          |                                     |   |
| Median (months)   | 16.7                                | 3.5   |
| Hazard Ratio  |                                     | 0.270   |
| 95% CI  |                                     | (0.17, 0.43)  |
| Adjusted p-value <sup>a</sup>   |                                     | <0.001  |

<sup>a</sup> Calculated from a weighted Holm's procedure

Pre-specified subgroup analyses of ORR4 per IRF were performed by patients' CTCL subtype, physicians' choice of treatment, baseline ECOG status, age, gender, and geographic region. The analyses showed a consistent trend towards benefit for patients who received brentuximab vedotin compared with patients who received physician's choice. ORR4 was 50% and 75% in the brentuximab vedotin arm versus 10.2% and 20% in the physician's choice arm for MF and pcALCL, respectively.

No meaningful differences in quality of life (assessed by the EuroQol five dimensions questionnaire [EQ-5D] and Functional Assessment of Cancer Therapy-General [FACT-G]) were observed between the treatment arms.

The efficacy and safety of ADCETRIS were evaluated in two additional open-label studies in 108 patients with relapsed CD30+ CTCL (including MF and pcALCL as well as SS, LyP and mixed CTCL histology), regardless of CD30 expression level. Patients were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles. The safety and efficacy results in these studies were consistent with results in Study C25001. Overall response rates for MF were 54-66%; pcALCL, 67%; SS, 50%; LyP, 92%; and mixed CTCL histology, 82-85%.

#### *Paediatric Population*

The safety, pharmacokinetics and anti-tumour activity of brentuximab vedotin in 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n=12 and adolescents aged 12 to 17 years, n=24) were evaluated in a phase 1/2 open-label, single-agent, multicentre dose-escalation study (C25002). Phase 1 of the study assessed the safety profile (see section 4.8), determined the paediatric maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and assessed the pharmacokinetics of brentuximab vedotin (see section 5.2). Phase 1 included 3 r/r HL patients treated at 1.4 mg/kg and 9 patients (7 r/r HL and 2 sALCL) treated at 1.8 mg/kg. The MTD was not reached. The RP2D was determined to be 1.8 mg/kg. Across the study, a total of 16 patients with r/r HL and 17 patients with r/r sALCL, of whom 10 were in first relapse, were treated with 1.8 mg/kg of

brentuximab vedotin. The best overall response rate (ORR) per independent review facility (IRF) was analysed across both study phases at the RP2D. Of these 33 patients who received the RP2D, 32 were evaluable for response. The ORR was 47% in response-evaluable patients with r/r HL, 53% in patients with r/r sALCL and 60% in sALCL patients in first relapse. Eight HL patients and 9 sALCL patients went on to receive SCT following treatment with brentuximab vedotin.

The European Medicines Agency has deferred the obligation to submit the results of studies with ADCETRIS in one or more subsets of the paediatric population in the treatment of Hodgkin lymphoma and treatment of anaplastic large cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion.

Maximum concentrations of brentuximab vedotin ADC were typically observed at the end of infusion or the sampling timepoint closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule, consistent with the terminal half-life estimate. Typical  $C_{max}$  and AUC of ADC after a single 1.8 mg/kg in a phase 1 study was approximately 31.98 µg/ml and 79.41 µg/ml x day respectively.

MMAE is the major metabolite of brentuximab vedotin. Median  $C_{max}$ , AUC and  $T_{max}$  of MMAE after a single 1.8 mg/kg of the ADC in a phase 1 study was approximately 4.97 ng/ml, 37.03 ng/ml x day and 2.09 days respectively. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses. MMAE is further metabolized mainly to an equally potent metabolite; however, its exposure is an order of magnitude lower than that of MMAE. Thus, it is not likely to have any substantial contribution to the systemic effects of MMAE.

In the first cycle, higher MMAE exposure was associated with an absolute decrease in neutrophil count.

### Distribution

*In vitro*, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound medicines. *In vitro*, MMAE was a substrate of P-gp and was not an inhibitor of P-gp at clinical concentrations.

In humans, the mean steady state volume of distribution was approximately 6-10 l for ADC. Based on population PK estimation the typical apparent volume of distribution (VM and VMP) of MMAE were 7.37 l and 36.4 l respectively.

### Metabolism

The ADC is expected to be catabolised as a protein with component amino acids recycled or eliminated.



*In vivo* data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. The levels of MMAE metabolites have not been measured in human plasma. At least one metabolite of MMAE has been shown to be active *in vitro*.

MMAE is a substrate of CYP3A4 and possibly CYP2D6. *In vitro* data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes indicate that MMAE inhibits only CYP3A4/5 at concentrations much higher than was achieved during clinical application. MMAE does not inhibit other isoforms.

MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

### Elimination

The ADC is eliminated by catabolism with a typical estimated CL and half life of 1.457 l/day and 4-6 days respectively.

The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half life of MMAE was 19.99 l/day and 3-4 days respectively.

An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of brentuximab vedotin. Approximately 24% of the total MMAE administered as part of the ADC during a brentuximab vedotin infusion was recovered in both urine and faeces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the faeces. A lesser amount of MMAE (28%) was excreted in the urine.

### Pharmacokinetics in special populations

Population PK analysis showed that baseline serum albumin concentration was a significant covariate of MMAE clearance. The analysis indicated that MMAE clearance was 2-fold lower in patients with low serum albumin concentrations <3.0 g/dl compared with patients with serum albumin concentrations within the normal range.

#### *Hepatic impairment*

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 2.3-fold (90% CI 1.27-4.12-fold) in patients with hepatic impairment.

#### *Renal impairment*

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (n=4), moderate (n=3) and severe (n=3) renal impairment. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold (90% CI 0.85-4.21-fold) in patients with severe renal impairment (creatinine clearance < 30 ml/min). No effect was observed in patients with mild or moderate renal impairment.

#### *Elderly*

The population pharmacokinetics of brentuximab vedotin were examined from several studies, including data from 380 patients up to 87 years old (34 patients  $\geq 65$ -<75 and 17 patients  $\geq 75$  years of age). The influence of age on pharmacokinetics was investigated and it was not a significant covariate (see section 4.2).

### Paediatric population

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 1.4 mg/kg or 1.8 mg/kg given every 3 weeks were evaluated in a phase 1/2 clinical trial of 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n=12 and adolescents aged 12 to 17 years, n=24) (see section 5.1). The  $C_{max}$  of ADC was typically observed at the end of infusion or the sampling closest to the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 5 days. Exposures were approximately dose proportional with a trend observed for lower ADC exposures at lower ages/ body weights in the study population. Median ADC AUC in children and adolescents from this study was approx. 14% and 3% lower than in adult patients, respectively, while MMAE exposures were 53% lower and 13% higher, respectively, than in adult patients. Median  $C_{max}$  and AUC of ADC after a single 1.8 mg/kg dose were 29.8 µg/mL and 67.9 µg\*day/mL, respectively, in patients <12 years of age and 34.4 µg/mL and 77.8 µg\*day/mL, respectively, in patients ≥12 years of age. Median  $C_{max}$ , AUC, and  $T_{max}$  of MMAE after a single 1.8 mg/kg dose were 3.73 ng/mL, 17.3 ng\*day/mL, and 1.92 days, respectively, in patients <12 years of age and 6.33 ng/mL, 42.3 ng\*day/mL, and 1.82 days, respectively, in patients ≥12 years of age. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged <12 years (0 of 11) and 2 patients aged ≥12 years (2 of 23) became persistently ADA positive.

### 5.3 Preclinical safety data

MMAE has been shown to have aneugenic properties in an *in vivo* rat bone marrow micronucleus study. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

The effects of brentuximab vedotin on human male and female fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. Testicular atrophy and degeneration were partially reversible following a 16-week treatment-free period.

Brentuximab vedotin caused embryo-foetal lethality in pregnant female rats.

In nonclinical studies, lymphoid depletion and reduced thymic weight were observed, consistent with the pharmacologic disruption of microtubules caused by MMAE derived from brentuximab vedotin.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Citric acid monohydrate  
Sodium citrate dihydrate  
α,α-Trehalose dihydrate  
Polysorbate 80

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

4 years.

After reconstitution/dilution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C.

#### **6.4 Special precautions for storage**

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

#### **6.5 Nature and contents of container**

Type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 50 mg powder.

Pack of 1 vial.

#### **6.6 Special precautions for disposal and other handling**

##### General precautions

Procedures for proper handling and disposal of anticancer medicines should be considered.

Proper aseptic technique throughout the handling of this medicinal product should be followed.

##### Instructions for reconstitution

Each single use vial must be reconstituted with 10.5 ml of water for injections to a final concentration of 5 mg/ml. Each vial contains a 10% overfill giving 55 mg of ADCETRIS per vial and a total reconstituted volume of 11 ml.

1. Direct the stream toward the wall of the vial and not directly at the cake or powder.
2. Gently swirl the vial to aid dissolution. DO NOT SHAKE.
3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6.6.
4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicinal product.

##### Preparation of infusion solution

The appropriate amount of reconstituted ADCETRIS must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ml ADCETRIS. The recommended diluent volume is 150 ml. The already reconstituted ADCETRIS can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing ADCETRIS. DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.

Do not add other medicinal products to the prepared ADCETRIS infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection.

Following dilution, infuse the ADCETRIS solution immediately at the recommended infusion rate.

Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

#### Determining dosage amount:

*Calculation to determine the total ADCETRIS dose (ml) to be further diluted (see section 4.2):*

$$\frac{\text{ADCETRIS dose (mg/kg)} \times \text{patient's body weight (kg)}}{\text{Reconstituted vial concentration (5 mg/ml)}} = \text{Total ADCETRIS dose (ml) to be further diluted}$$

Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximal recommended dose is 180 mg.

*Calculation to determine the total number of ADCETRIS vials needed:*

$$\frac{\text{Total ADCETRIS dose (ml) to be administered}}{\text{Total volume per vial (10 ml/vial)}} = \text{Number of ADCETRIS vials needed}$$

Table 13: Sample calculations for patients receiving the recommended dose of 1.8 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg

| <b>Patient weight (kg)</b> | <b>Total dose = patient weight multiplied by recommended dose [1.8 mg/kg<sup>a</sup>]</b> | <b>Total volume to be diluted<sup>b</sup> = total dose divided by reconstituted vial concentration [5 mg/ml]</b> | <b>Number of vials needed = total volume to be diluted divided by total volume per vial [10 ml/vial]</b> |
|----------------------------|---|--|--|
| 60 kg                      | 108 mg  | 21.6 ml  | 2.16 vials   |
| 80 kg                      | 144 mg  | 28.8 ml  | 2.88 vials   |
| 100 kg                     | 180 mg  | 36 ml  | 3.6 vials  |
| 120 kg <sup>c</sup>        | 180 mg <sup>d</sup>   | 36 ml  | 3.6 vials  |

- For a reduced dose, use 1.2 mg/kg for the calculation.
- To be diluted in 150 ml of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
- If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
- The maximal recommended dose is 180 mg.

#### Disposal

ADCETRIS is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S  
Dybendal Alle 10  
2630 Taastrup  
Denmark

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/794/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorization: 25 October 2012

Date of renewal: 10 November 2017

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

Piramal Healthcare UK Ltd.  
Earls Road, Grangemouth  
Stirlingshire, Scotland FK3 8XG  
United Kingdom

Lonza AG  
Lonzastrasse  
3930 Visp  
Switzerland

Name and address of the manufacturers responsible for batch release

Takeda Austria GmbH  
St. Peter-Straße 25  
A-4020 Linz  
Austria

Delpharm Novara S.r.l.  
Via Crosa, 86  
28065 Cerano (NO)  
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING  
AUTHORISATION**

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| <b>Description</b>   | <b>Due date</b>                |
|--|--------------------------------|
| Provision of the results of the ongoing Non-Interventional Post-Authorization Safety Study (PASS) conducted in HL and sALCL patient populations (Study MA25101).   | Final study report: 31/12/2020 |
| To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006). | Final Study Report by: Q1 2021 |



**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

ADCETRIS 50 mg powder for concentrate for solution for infusion  
brentuximab vedotin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 50 mg of brentuximab vedotin

After reconstitution each vial contains 5 mg/ml of brentuximab vedotin

**3. LIST OF EXCIPIENTS**

Excipients: Citric acid monohydrate, sodium citrate dihydrate,  $\alpha,\alpha$ -trehalose dihydrate, polysorbate 80  
See package leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

*Powder for concentrate for solution for infusion*

1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after reconstitution and dilution  
Read the package leaflet

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator  
Do not freeze  
Keep the vial in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

For single use only

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S  
Dybendal Alle 10  
2630 Taastrup  
Denmark

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/794/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

*Justification for not including Braille accepted*

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

ADCETRIS 50 mg powder for concentrate for solution for infusion  
brentuximab vedotin  
IV use

**2. METHOD OF ADMINISTRATION**

For intravenous use after reconstitution and dilution

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

50 mg

**6. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Adcetris 50 mg powder for concentrate for solution for infusion brentuximab vedotin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Adcetris is and what it is used for
2. What you need to know before you are given Adcetris
3. How Adcetris will be given
4. Possible side effects
5. How to store Adcetris
6. Contents of the pack and other information

#### 1. What Adcetris is and what it is used for

Adcetris contains the active substance **brentuximab vedotin**, an anti-cancer agent, which is made up of a monoclonal antibody linked to a substance intended to kill cancer cells. This substance is delivered to cancer cells by the monoclonal antibody. A monoclonal antibody is a protein which recognises certain cancer cells.

Adcetris is used to treat classical Hodgkin lymphoma that has:

- come back after or not responded to an infusion of your own healthy stem cells into your body (autologous stem cell transplant), or
- come back after or never responded to at least two previous therapies, and where you cannot receive additional combination anti-cancer treatments or have an autologous stem cell transplant.

Classical Hodgkin lymphoma expresses specific proteins on the cell surface that are different from non-classical Hodgkin lymphoma.

Adcetris is also used to lower the likelihood of classical Hodgkin Lymphoma coming back after an autologous stem cell transplant in patients with certain risk factors.

Adcetris is used to treat systemic anaplastic large cell lymphoma which is found in your lymph nodes and/or throughout other parts of your body that has:

- not responded to other types of anti-cancer treatments, or
- come back after previous anti-cancer treatment.

Hodgkin lymphoma and systemic anaplastic large cell lymphoma are both types of cancer of the white blood cells.

Adcetris is used to treat cutaneous T-cell lymphoma (CTCL) in patients who have previously received at least one medicine that travels through the bloodstream.

CTCL is a cancer of a certain type of white blood cell called a 'T-cell' that mainly affects the skin. Adcetris is used to treat CTCL where a specific type of protein is present on the cells' surface.

## 2. What you need to know before you are given Adcetris

### Do NOT use Adcetris if you:

- are allergic to brentuximab vedotin or any of the other ingredients of this medicine (listed in section 6).
- are currently using bleomycin, an anti-cancer agent

### Warnings and precautions

When you first receive this medicine and during the course of treatment, tell your doctor if you:

- have confusion, trouble thinking, memory loss, blurred or loss of vision, decreased strength, decreased control or sensation in one arm or leg, a change in the way of walking, or loss of balance, as these may be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). If you have these symptoms prior to treatment with this medicine, tell your doctor immediately about any changes in these symptoms. You should also inform your partner or caregivers about your treatment, since they may notice symptoms that you are not aware of.
- have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas).
- have new or worsening shortness of breath or cough as these may be symptoms of a serious and potentially fatal lung complication (pulmonary toxicity)
- are taking, or have previously taken, medicines which may affect your immune system, such as chemotherapy or immunosuppressive agents
- have, or think you have, an infection. Some infections may be serious and can be due to viruses, bacteria, or other causes that may be life-threatening
- experience a whistling sound during breathing (wheezing)/difficulty breathing, hives, itching, or swelling (signs of an infusion reaction). For more detailed information, see "Infusion reactions" in section 4.
- have any problems with a change in the sensitivity of the skin, especially in the hands or feet, such as numbness, tingling, a burning sensation, pain, discomfort or weakness (neuropathy)
- have headaches, feel tired, experience dizziness, look pale (anaemia), or have unusual bleeding or bruising under the skin, longer than usual bleeding after your blood has been drawn, or bleeding from your gums (thrombocytopenia)
- develop chills or shivering, or feel warm; you should take your temperature as you may have a fever. A fever with a low white blood cell count may be a sign of serious infection
- experience dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances (this may be a potentially life-threatening complication known as tumour lysis syndrome)
- experience flu-like symptoms followed by a painful red or purplish rash that spreads and blisters including extensive detachment of the skin that may be life-threatening (this may be a serious skin reaction known as Stevens-Johnson syndrome and toxic epidermal necrolysis)
- have new or worsening stomach pain, nausea, vomiting, constipation as these may be symptoms of a serious and potentially fatal stomach or intestinal complication (gastrointestinal complications)
- have abnormal liver test results as this may be related to a serious and potentially fatal liver injury (hepatotoxicity). Liver disease and other medical conditions that may have been present before you start taking Adcetris and some medications that you are currently taking might increase the risk of liver injury.
- feel tired, have frequent urination, increased thirst, increased appetite with unintended weight loss, or irritability (hyperglycaemia)
- have kidney or liver problems.



Your doctor will perform regular blood tests to make sure that it is safe for you to receive this medicine.

### **Other medicines and Adcetris**

Tell your doctor if you are taking any other medicines, if you have taken any recently, or if you start taking new ones. This includes herbal medicines and other medicines you can obtain without a prescription.

### **Pregnancy, breast-feeding and fertility**

You and your partner must use two methods of effective contraception during your treatment with this medicine. Women must continue using contraception for 6 months following the last dose of Adcetris.

You should not use this medicine if you are pregnant unless you and your doctor decide that the benefit to you outweighs the potential risk to the unborn baby.

It is important to tell your doctor before and during treatment if you are pregnant, think you may be pregnant, or are planning to get pregnant.

If you are breast-feeding, you should discuss with your doctor whether you should receive this medicine.

Men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men are advised not to father a child during treatment with this medicine and for up to 6 months following the last dose of this medicine.

### **Driving and using machines**

Your treatment may influence your ability to drive or operate machines. If you feel unwell during treatment then do not drive or operate machines.

### **Adcetris contains sodium**

This medicine contains a maximum of 2.1 mmol (or 47 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

## **3. How Adcetris will be given**

If you have any questions on the use of this medicine, ask the doctor or nurse who is giving you the infusion.

### **Dose and frequency**

The dose of this medicine depends on your body weight. The usual starting dose of Adcetris is 1.8 mg/kg, given once every 3 weeks for no more than one year. Your doctor may lower your starting dose to 1.2 mg/kg if you have kidney or liver problems.

Adcetris is to be given to adults only. It is not for use in children.

### **How Adcetris is given**

This medicine is given to you into a vein (intravenously) as an infusion. It is given by your doctor or nurse over 30 minutes. Your doctor or nurse will also monitor you during and after the infusion.

If you have any other questions on the use of this medicine, ask your doctor.

#### **4. Possible side effects**

Like all medicines, this medicine may cause side effects, although not everybody gets them.

##### **Infusion reactions**

Medicines of this type (monoclonal antibodies) can cause infusion reactions such as:

- a rash
- shortness of breath
- difficulty breathing
- cough
- a tight chest
- fever
- back pain
- chills
- headache
- feeling sick (nausea) or being sick (vomiting).

Infusion reactions to this medicine affect more than 1 in 10 people.

In general, these types of reactions occur within minutes to several hours following completion of the infusion. However, they may develop more than several hours after completion of the infusion but this is uncommon. These infusion reactions can be serious or even fatal (known as an anaphylactic reaction). It is not known how frequently infusion-related reactions to this medicine are serious or fatal.

You may be given other medicines such as

- anti-histamines, corticosteroids or paracetamol

to help reduce any of the reactions above if you have already experienced these when receiving this type of medicine.

If you think you have previously had a similar reaction, tell your doctor BEFORE you are given this medicine.

If you develop infusion reactions (as stated previously), your doctor may stop giving this medicine and start support treatment.

If your infusion is restarted, your doctor may increase the time over which your infusion is given so that you may be able to tolerate it better.

**Tell your doctor straight away if you notice any of the following symptoms because some of them may be signs of a serious or possibly fatal condition:**

- progressive multifocal leukoencephalopathy (PML) symptoms such as confusion, trouble thinking, memory loss, blurred or loss of vision, decreased strength, decreased control or sensation in one arm or leg, a change in the way of walking, or loss of balance (for more detailed information, see section 2) (affects less than 1 in 100 people)
- symptoms of inflammation of the pancreas (pancreatitis) such as severe and persistent stomach pain, with or without nausea and vomiting (affects less than 1 in 100 people).
- shortness of breath or cough (affects more than 1 in 10 people)
- flu-like symptoms followed by a painful red or purplish rash that spreads and blisters including extensive detachment of the skin (affects less than 1 in 100 people)
- a change in feeling or sensitivity, especially in the skin, numbness, tingling, discomfort, a burning sensation, weakness, or pain in the hands or feet (neuropathy; affects more than 1 in 10 people)
- a feeling of weakness (affects more than 1 in 10 people)
- constipation (affects more than 1 in 10 people)

- diarrhoea, vomiting (affects more than 1 in 10 people)
- chills or shivering (affects less than 1 in 10 people)
- feeling tired, frequent urination, increased thirst, increased appetite with unintended weight loss, and irritability (these may be signs of hyperglycaemia, which affects less than 1 in 10 people)
- unusual bleeding or bruising under the skin, longer than usual bleeding after your blood has been drawn, or bleeding from your gums (these may be signs of thrombocytopenia which affects less than 1 in 10 people)
- headaches, experience dizziness, look pale (these may be signs of anaemia, which affects less than 1 in 10 people)

You may experience the following side effects:

**Very common side effects** (affects more than 1 in 10 people)

- decreased level of white blood cells
- upper respiratory tract infection
- decrease in weight
- infection
- nausea
- abdominal pain
- itching
- muscle pain
- joint pain or painful, swollen joints

**Common side effects** (affects less than 1 in 10 people)

- pneumonia
- sore, creamy-yellow, raised patches in the mouth (thrush)
- decreased level of blood platelets
- dizziness
- blisters which may crust or scab
- increased level of blood sugar
- increased liver enzyme levels
- unusual hair loss or thinning

**Uncommon side effects** (affects less than 1 in 100 people)

- Tumour lysis syndrome – a potentially-life threatening condition in which you may experience dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances.
- new or recurring cytomegalovirus (CMV) infection
- an infection in the blood (sepsis) and/or septic shock (a life-threatening form of sepsis)
- Stevens-Johnson syndrome and toxic epidermal necrolysis - a rare, serious disorder in which you may experience flu-like symptoms followed by a painful red or purplish rash that spreads and blisters including extensive detachment of the skin
- decreased level of white blood cells with a fever
- damage to the nerves and nerve coverings (demyelinating polyneuropathy)

### Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Adcetris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and the carton after EXP. The expiry date refers to the last day of that month.

**Unopened vial:** Store in a refrigerator (2°C-8°C). Do not freeze.  
Keep the vial in the original carton in order to protect from light.

**Reconstituted/diluted solution:** Use immediately or store in a refrigerator (2°C-8°C) and use within 24 hours.

Do not use this medicine if you notice any particulate matter or discoloration prior to administration.

Do not throw away any medicines via wastewater or household waste. The doctor or nurse will dispose of this medicine. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Adcetris contains

- The active substance is brentuximab vedotin. Each vial contains 50 mg of brentuximab vedotin. After reconstitution each ml of solution contains 5 mg of Adcetris.
- The other ingredients are citric acid monohydrate, sodium citrate dihydrate,  $\alpha,\alpha$ -trehalose dihydrate, and polysorbate 80. See section 2 for further information about sodium.

### What Adcetris looks like and contents of the pack

Adcetris is a white to off-white cake or powder for concentrate for solution for infusion provided in a glass vial.

Each pack of Adcetris consists of one vial.

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**This leaflet was last revised in**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu/>

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The following information is intended for healthcare professionals only:

**Instructions for reconstitution**

Each single use vial must be reconstituted with 10.5 ml of water for injections to a final concentration of 5 mg/ml. Each vial contains a 10% overfill giving 55 mg of Adcetris per vial and a total reconstituted volume of 11 mL.

1. Direct the stream toward the wall of the vial and not directly at the cake or powder.
2. Gently swirl the vial to aid dissolution. DO NOT SHAKE.
3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6.6.
4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicinal product.

**Preparation of Infusion Solution**

The appropriate amount of reconstituted Adcetris must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ml Adcetris. The recommended diluent volume is 150 ml. The already reconstituted Adcetris can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing Adcetris. DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.

Do not add other medicinal products to the prepared Adcetris infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection.

Following dilution, infuse the Adcetris solution immediately at the recommended infusion rate.

Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

### **Disposal**

Adcetris is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.