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 relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

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.

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 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).

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

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

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

b. 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

Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAE[a]])	**Modification of dose and schedule**
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 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

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

Older patients

The safety and efficacy in older patients aged 65 and older have not been established. No data are available.

Paediatric population

The safety and efficacy of children less than 18 years have not yet been established. No data are available.

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 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.

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, and opportunistic infections such as Pneumocystis jiroveci 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 infusion-related reaction 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 infusion-related reaction should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

Infusion-related reactions 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 a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In the phase 2 population, at the time of last evaluation, the majority of patients (62%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 9%, dose reductions were reported in 8%, and dose delays occurred in 13% of patients. 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 (≥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 ≥38.5°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.

Hepatic function

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported. Liver function should be routinely monitored in patients receiving 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).

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; however it reduced exposure to MMAE by approximately 31%.

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.

Serious infections and opportunistic infections have been reported in patients treated with this medicine (see section 4.4). In the phase 2 population, 16% of patients reported an event term that referred to an infection.

Serious adverse drug reactions in the phase 2 population were: neutropenia, thrombocytopenia, constipation, diarrhoea, vomiting, pyrexia, peripheral motor neuropathy and peripheral sensory neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.

The most frequently observed adverse reactions in the phase 2 population were: peripheral sensory neuropathy, fatigue, nausea, diarrhoea, neutropenia, vomiting, pyrexia, and upper respiratory tract infection.

In the phase 2 population, adverse reactions led to treatment discontinuation in 19% of patients receiving brentuximab vedotin. Serious adverse reactions that led to treatment discontinuation in two or more HL or sALCL patients were peripheral sensory neuropathy (6%) and peripheral motor neuropathy (2%).

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 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 (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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
Infections and infestations	
Very common:	Infection[a]
Common:	Sepsis/septic shock, upper respiratory tract infection, herpes zoster, pneumonia
Uncommon:	Oral candidiasis, Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia
Frequency not known:	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	
Very common:	Neutropenia
Common:	Anaemia, thrombocytopenia
Frequency not known:	Febrile neutropenia
Immune system disorders	
Frequency not known:	Anaphylactic reaction
Metabolism and nutrition disorders	
Common	Hyperglycaemia
Uncommon:	Tumour lysis syndrome
Nervous system disorders	
Very common:	Peripheral sensory neuropathy
Common:	Peripheral motor neuropathy, dizziness, demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Gastro-intestinal disorders	
Very common:	Diarrhoea, nausea, vomiting
Common:	Constipation
Uncommon:	Pancreatitis acute
Hepatobiliary disorders	
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus
Common:	Rash
Rare:	Stevens-Johnson syndrome/toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia
Common:	Arthralgia, back pain
General disorders and administration site conditions	
Very common:	Fatigue, pyrexia, infusion-related reactions[b]
Common:	Chills

a. Preferred terms that were reported under the Infections and Infestations SOC include sepsis/septic shock, upper respiratory tract infection, herpes zoster, and pneumonia.

b. Preferred terms associated with infusion-related reactions were chills (4%), nausea, dyspnoea and pruritus (3% each), and cough (2%).

Description of selected adverse reactions

Adverse reactions that led to dose delays of up to 3 weeks in more than 5% of patients were neutropenia (14%) and peripheral sensory neuropathy (11%) (see section 4.2).

The adverse reaction that led to a dose reduction in more than 5% of patients was peripheral sensory neuropathy (8%). Ninety percent (90%) of patients in the phase 2 studies remained at the recommended dose of 1.8 mg/kg while on treatment.

Severe and prolonged (≥1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. The median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥7 days. Less than half of the patients in the 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.

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 10 weeks. At the time of last evaluation, 62% of the 84 patients 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 was 6.6 weeks (range from 0.3 weeks to 54.4 weeks).

PML has been reported outside of the pivotal phase 2 clinical trials (see section 4.4).

Acute pancreatitis (including fatal outcomes) has been reported outside of the pivotal phase 2 clinical trials. Consider the diagnosis of acute pancreatitis for patients presenting with new or worsening abdominal pain (see section 4.4).

Anaphylactic reactions have been reported outside of the pivotal phase 2 clinical trials (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Febrile neutropenia has been reported outside of the pivotal phase 2 clinical trials (see section 4.2). A patient enrolled in a phase 1 dose escalation trial experienced Grade 5 febrile neutropenia after receiving a single dose of 3.6 mg/kg of brentuximab vedotin.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin in clinical trials and post-marketing use. Fatal outcomes have been reported (see section 4.4).

Immunogenicity

Patients with relapsed or refractory HL or sALCL in two phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 35% of patients in these studies developed antibodies to brentuximab vedotin. Of these patients, the majority became positive prior to dose 2, 7% were persistently anti-therapeutic antibodies (ATA)-positive, and 62% of the ATA-positive patients had neutralizing antibodies. One (1) percent of patients experienced adverse reactions consistent with infusion-related reactions that led to discontinuation of treatment.

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 ATA (30%) relative to patients with transiently positive ATA (12%) and never positive ATA (7%).

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 and sALCL 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 and sALCL disease and therapeutic spectrums and clinical evidence in two CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL and sALCL with or without prior ASCT. 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

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in a pivotal open-label, single-arm, multicenter study (study SG035-0003) 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

Patient characteristics	**N = 102**
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%)
Disease characteristics	
Primary Refractory to frontline therapy[a]	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%)

[a.] 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 32.7 months). The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 7 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

Best clinical response (N = 102)	**IRF N (%)**	**95% CI**
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
Duration of response	**Median per IRF**	**95% CI**
Objective response rate (CR + PR) [a]	6.7 months	3.6, 14.8
Complete remission (CR)	Not reached	10.8, NE[b]
Overall survival	**Median**	**95% CI**
Median	40.5 months	28.7, NE

a. The range of DOR was1.2+ months to 26.1+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 9.0 months.

b. 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 were 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.

Systemic anaplastic large cell lymphoma

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in an open-label, single-arm, multicenter study (study SG035-0004) in 58 patients with relapsed or refractory sALCL. See Table 6 below for a summary of baseline patient and disease characteristics.

Table 6: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study

Patient characteristics	**N = 58**
Median age, yrs (range)	52 years (14-76)
Gender	33M (57%)/25F (43%)
ECOG status[a]	
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%)
Disease characteristics	
Primary Refractory to frontline therapy[b]	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 was achieved in 97% of patients. The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 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 7 responding patients went on to autologous SCT. For further efficacy results, see Table 7.

Table 7: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks

Best clinical response (N = 58)	**IRF N (%)**	**95% CI**
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
Duration of response	**Median per IRF**	**95% CI**
Objective response (CR + PR)[a]	13.2	5.7, NE[b]
Complete remission (CR)	Not reached	13.0, NE
Overall survival	**Median**	**95% CI**
Median	Not reached[c]	21.3, NE

a. The range of DOR was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.

b. Not estimable.

c. The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 months).

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.

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.

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.

Older patients

Clinical studies of brentuximab vedotin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Paediatric population

Clinical studies of brentuximab vedotin did not include sufficient numbers of patients below 18 years of age to determine whether the PK profile differs from adult patients.

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

3 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):

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

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

Patient weight (kg)	**Total dose = patient weight multiplied by recommended dose [1.8 mg/kg[a]])**	**Total volume to be diluted[b] = total dose divided by reconstituted vial concentration [5 mg/ml])**	**Number of vials needed = total volume to be diluted divided by total volume per vial [10 ml/vial])**
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[c]	*180 mg[d]*	*36 ml*	*3.6 vials*

a. For a reduced dose, use 1.2 mg/kg for the calculation.
b. To be diluted in 150 ml of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
c. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
d. 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
Langebjerg 1
DK-4000 Roskilde
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: 26 August 2013

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 MANUFACTURER 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 MANUFACTURER 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 manufacturer responsible for batch release

Takeda Italia S.p.A.
Via Crosa, 86
28065 Cerano (NO)
Italy

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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:

Description	**Due date**
Further Overall Survival follow up of the patients included in study SG035-004 should be provided, including sub-analysis of patients ≥ 100 kg. The data should be presented in the context of historical controls.	SG035-004 annual reports until 2016 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier
A Non-interventional Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).	Final study report: 31/12/2018
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 2016
To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol.	Final study report by: Q2 2016

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, α,α-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
Langebjerg 1
DK-4000 Roskilde
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

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 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.

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
- 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)
- 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
- a tight chest
- fever
- back pain.

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). The frequency of this condition cannot be estimated from the available data.
- 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).
- 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 1000 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 less 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
- infection
- nausea
- itching
- unusual hair loss or thinning
- muscle pain

Common side effects (affects less than 1 in 10 people)
- an infection in the blood (sepsis) and/or septic shock (a life-threatening form of sepsis);cough; upper respiratory tract infection; pneumonia
- decreased level of blood platelets
- dizziness
- joint pain or painful, swollen joints
- blisters which may crust or scab
- increased level of blood sugar
- increased liver enzyme levels

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.
- sore, creamy-yellow, raised patches in the mouth (thrush)

Rare side effects (affects less than 1 in 1000 people)
- 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

Not known (frequency cannot be estimated from the available data)
- decreased level of white blood cells with a fever

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, α,α-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.

Marketing Authorisation Holder

Takeda Pharma A/S
Langebjerg 1
DK-4000 Roskilde
Denmark

Manufacturer

Takeda Italia S.p.A.
Via Crosa, 86
28065 Cerano (NO)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgium
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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/

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.