PRODUCT MONOGRAPH

[Pr]ADCETRIS®
(brentuximab vedotin)

Lyophilized powder for reconstitution with 10.5 mL of sterile Water for Injection, USP
50 mg

Antineoplastic agent

ADCETRIS has been issued conditional marketing authorization for:

- **the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates**
- **the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen**

These marketing authorizations are conditional, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ADCETRIS, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

ADCETRIS has been issued non-conditional marketing authorization for:

- **the post-ASCT consolidation treatment of patients with HL at increased risk* of relapse or progression.**

**See Part II, Clinical Trials*

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Date of Approval: June 19, 2018

Canadian importer/distributor:

McKesson Specialty Distribution Inc.

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Submission Control No: 215496

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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[Pr]ADCETRIS®
(brentuximab vedotin)

PART I: HEALTH PROFESSIONAL INFORMATION

ADCETRIS has been issued conditional marketing authorization for:

- the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates
- the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen

These marketing authorizations are conditional, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

ADCETRIS has been issued non-conditional marketing authorization for:

- the post-ASCT consolidation treatment of patients with HL at increased risk* of relapse or progression.

**See Part II, Clinical Trials*

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder, 50 mg	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the potent microtubule-disrupting agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, 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 tumor cell.

INDICATIONS AND CLINICAL USE

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate indicated for:

NOC/c The treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.

Clinical effectiveness in relapsed or refractory HL was based on promising response rates demonstrated in single-arm trials (*see CLINICAL TRIALS*). No data demonstrate increased survival with ADCETRIS.

NOC/c The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen.

Clinical effectiveness in relapsed or refractory sALCL was based on promising response rates demonstrated in single-arm trials (*see CLINICAL TRIALS*). No data demonstrate increased survival with ADCETRIS.

NOC The post-ASCT consolidation treatment of patients with HL at increased risk* of relapse or progression *(* see Part II, Clinical Trials).*

ADCETRIS should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy.

Geriatrics (≥65 years of age):
The safety and efficacy of ADCETRIS have not been established in the geriatric population.

Pediatrics (<18 years of age):
The safety and efficacy of ADCETRIS have not been established in the pediatric population.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *Dosage Forms, Composition and Packaging* section of the product monograph.

- Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity.
- ADCETRIS is contraindicated for patients who have or have had progressive multifocal leukoencephalopathy (PML) (*See WARNINGS AND PRECAUTIONS, Progressive Multifocal Leukoencephalopathy*).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Clinically significant and/or life-threatening adverse events include:

- JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death (*see WARNINGS AND PRECAUTIONS, Progressive Multifocal Leukoencephalopathy*)
- Stevens-Johnson syndrome and toxic epidermal necrolysis (*see WARNINGS AND PRECAUTIONS, Dermatologic*)
- Serious and opportunistic infections (*see WARNINGS AND PRECAUTIONS, Infections*)
- Acute pancreatitis (see *WARNINGS AND PRECAUTIONS, Gastrointestinal)*
- Gastrointestinal complications *(see WARNINGS AND PRECAUTIONS, Gastrointestinal)*
- Pulmonary toxicity *(see WARNINGS AND PRECAUTIONS, Pulmonary)*

General

Infusion reactions

Immediate and delayed infusion-related reactions, as well as anaphylaxis, have been reported. Carefully monitor patients during and after infusion of ADCETRIS. Symptoms of an infusion reaction include chills, nausea, cough, and itching within 2 days after a dose. Symptoms of a severe infusion reaction include wheezing, difficulty breathing, syncope, hives, itching, and swelling. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine and a corticosteroid. In clinical trials, IRRs were reported more frequently and with more severity in patients who developed anti-drug antibodies (*see ADVERSE REACTIONS, Clinical Trials Adverse Reactions, Immunogenicity).*

Cardiac Ventricular Repolarization

QT shortening was observed in CD30-positive patients treated with brentuximab vedotin. The clinical significance of QT shortening is unknown.

Dermatologic

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. The symptoms of SJS and TEN include unexplained widespread skin pain, blisters on the skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of the skin. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

Gastrointestinal

Acute pancreatitis, including fatal outcomes, has been reported in patients treated with ADCETRIS. Consider the diagnosis of acute pancreatitis for patients presenting with new or worsening abdominal pain. Hold ADCETRIS for any suspected case of acute pancreatitis and discontinue if a diagnosis of acute pancreatitis is confirmed.

Gastrointestinal (GI) complications, including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and hemorrhage, some with fatal outcomes, have been reported in patients treated with ADCETRIS. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Hematologic

Anemia: Grade 3 or 4 anemia can occur with ADCETRIS.

Neutropenia and Febrile Neutropenia: Prolonged (≥1 week) severe neutropenia and febrile neutropenia can occur with ADCETRIS. In clinical trials, neutropenia of any grade occurred in the majority of ADCETRIS-treated patients (*See ADVERSE REACTIONS, Clinical Trial Adverse Reactions*). Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. Patients with Grade 3 or 4 neutropenia should be closely monitored for fever and managed by growth factor support, dose delays, reductions or discontinuations (*see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS, Clinical Trials Adverse Reactions).*

Thrombocytopenia: Prolonged (≥1 week) severe thrombocytopenia can occur with ADCETRIS. If Grade 3 or 4 thrombocytopenia develops, monitor closely and consider platelet transfusions or dose delays.

Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

Hyperglycemia

Hyperglycemia has been reported during clinical trials in patients with an elevated body mass index (BMI) with or without a history of diabetes mellitus. If hyperglycemia develops, monitor the patient's serum glucose and administer anti-diabetic treatment as appropriate.

Immune

The efficacy and safety of, and ability to generate a primary or anamnestic response to immunization with live attenuated or inactivated vaccines during or following ADCETRIS treatment have not been established; therefore, patients should be observed for failure to respond to a vaccine. The risks and benefits of vaccinating patients with live attenuated, or inactivated, vaccines during or following ADCETRIS therapy should be considered.

Infections

Serious and opportunistic infections such as pneumonia, bacteremia, sepsis/septic shock (including fatal outcomes), herpes zoster, cytomegalovirus (reactivation), Pneumocystis jiroveci pneumonia, and oral candidiasis have been reported in patients treated with ADCETRIS. Symptoms of infection include fever (≥38°C), sore throat, difficulty breathing, painful sores (ulcers) around the mouth and/or anus, or pain on urination. Patients should be carefully monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

Neurologic

Peripheral Neuropathy

ADCETRIS treatment can cause peripheral neuropathy, both sensory and motor. Monitor patients 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, change in dose, or discontinuation of ADCETRIS *(See DOSAGE AND ADMINISTRATION*).

In clinical trials, over half of ADCETRIS-treated patients experienced any grade of neuropathy. ADCETRIS-induced peripheral neuropathy is typically associated with cumulative exposure and is often reversible following cessation of treatment. The majority of patients who developed peripheral neuropathy experienced partial improvement or complete resolution at the end of treatment or during long-term follow-up. Time from onset to improvement or resolution increased with greater severity of neuropathy (*See ADVERSE REACTIONS, Clinical Trials Adverse Reactions*).

Progressive multifocal leukoencephalopathy

JC virus (JCV) infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in ADCETRIS-treated patients. Contributing factors may include prior therapies and underlying disease that may cause immunosuppression.

Closely monitor patients for any new or worsening neurological, cognitive, or psychiatric signs or symptoms suggestive of PML. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. Hold ADCETRIS dosing for any suspected case of PML and initiate neurology consultation for evaluation of PML, which includes magnetic resonance imaging of the brain and cerebrospinal fluid analysis or a brain biopsy for evidence of JCV. Discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Pulmonary

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported in ADCETRIS-treated patients, either as single-agent or in combination with bleomycin. Concomitant use of ADCETRIS and bleomycin is contraindicated. Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. In the event of new or worsening pulmonary symptoms, a

prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding ADCETRIS dosing during evaluation and until symptomatic improvement.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported. Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of TLS. Symptoms of TLS include nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and acute renal failure. Monitor at-risk patients closely and take prophylactic or treatment measures, as appropriate. Prophylaxis and treatment for TLS may include hydration, correction of electrolyte abnormalities, and anti-hyperuricemic agents. In severe cases of TLS, hemodialysis or hemofiltration may be required.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies performed with ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities including increased early resorption, post-implantation loss, decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs) in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. Brentuximab vedotin and MMAE were both shown to cross the placenta in this study (*see Part II, Developmental and Reproductive Toxicity*).

For women of childbearing potential, precautions should be taken to avoid pregnancy and at least two contraceptive methods should be used while taking ADCETRIS and for 6 months after completing therapy. If pregnancy occurs, the physician should be immediately informed. ADCETRIS should not be administered to pregnant women unless the possible benefits to the mother outweigh the risks to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

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

Nursing Women

It is not known whether brentuximab vedotin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility
It is not known if ADCETRIS will affect human spermatogenesis. In non-clinical studies, brentuximab vedotin resulted in testicular toxicity which was partially resolved 16-weeks post last dose administration. Therefore, due to this potential risk, men should be advised not to impregnate their partner during treatment with ADCETRIS. Men of reproductive potential should use an appropriate method of barrier contraception throughout treatment with ADCETRIS and for at least 6 months after completing therapy (see *Developmental and Reproductive Toxicity: Impairment of Fertility*).

Pediatrics (<18 years of age)
The safety and efficacy of ADCETRIS have not been established in the pediatric population. Clinical trials of ADCETRIS included only 9 pediatric patients and this number is not sufficient to determine whether they respond differently than adult patients (*see ACTION AND CLINICAL PHARMACOLOGY*).

Geriatrics (≥65 years of age)
The safety and efficacy of ADCETRIS have not been established in the geriatric population. Clinical trials of ADCETRIS included 17 geriatric patients and this number is not sufficient to determine whether they respond differently than younger patients (*see ACTION AND CLINICAL PHARMACOLOGY*).

Renal impairment
Avoid use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CLcr) <30 mL/min]. MMAE exposure is increased in patients with severe renal impairment. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function (*see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY*).

Hepatic impairment
Avoid use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. In patients with mild hepatic impairment, start ADCETRIS at a reduced dose of 1.2 mg/kg and closely monitor for adverse reactions. MMAE exposure is increased in patients with hepatic impairment. Due to higher MMAE exposure, ≥Grade 3 adverse reactions and deaths may be more frequent in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function (*see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY*).

Monitoring and Laboratory Tests

Complete blood counts should be monitored prior to each dose of ADCETRIS and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia or thrombocytopenia.

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials (Studies 1 and 2). Across both trials, the most common treatment emergent adverse reactions (≥20%), regardless of causality, were peripheral sensory neuropathy, fatigue, nausea, diarrhea, anemia, pyrexia, upper respiratory tract infection, neutropenia, vomiting and cough. The most common adverse reactions occurring in at least 5% of patients in either trial, regardless of causality, using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, are shown in Table 1.

ADCETRIS was administered as monotherapy in 167 of 329 patients in a randomized, placebo-controlled phase 3 trial in patients with HL at increased risk of relapse or progression following ASCT (Study 3). The most common treatment emergent adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea. The most common adverse reactions occurring in at least 5% of patients in the ADCETRIS arm and at a higher rate than the placebo arm, regardless of causality, using the NCI CTCAE Version 4.0, are shown in Table 3.

Clinical Trial Adverse Drug Reactions

NOC/c Adverse Reactions in Relapsed/Refractory HL and sALCL Pivotal Trials (Studies 1 and 2)

ADCETRIS was studied in 102 patients with HL (Study 1) and 58 patients with sALCL (Study 2) in single arm pivotal, phase 2 trials in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks for a maximum of 16 cycles. Median durations of

treatment were 27 weeks (range, 3 to 56 weeks) and 23.5 weeks (range, 3 to 75 weeks) for the HL and sALCL studies, respectively (*see Clinical Trials section).*

The treatment-emergent adverse reactions that occurred in ≥20% of HL patients in Study 1 were: leukopenia (61%), neutropenia (54%), peripheral sensory neuropathy (52%), upper respiratory tract infection (47%), fatigue (46%), nausea (42%), diarrhea (36%), anemia (33%), pyrexia (29%), thrombocytopenia (28%), lymphopenia (24%), vomiting (22%), and cough (21%). Grade 3 treatment-emergent adverse reactions that occurred in more than 2% of patients included neutropenia (15%), peripheral sensory neuropathy (9%), anemia (8%), thrombocytopenia (7%), lymphopenia (7%), leukopenia (6%), and peripheral motor neuropathy (4%). Grade 4 treatment-emergent adverse reactions included neutropenia (6%), thrombocytopenia (2%), anemia (2%), abdominal pain (1%) and lymphopenia (1%).

The treatment-emergent adverse reactions that occurred in ≥20% of systemic ALCL patients in Study 2 were: neutropenia (64%), leukopenia (52%), peripheral sensory neuropathy (52%), nausea (40%), fatigue (38%), pyrexia (34%), anemia (33%), diarrhea (29%), upper respiratory tract infection (28%), lymphopenia (26%), rash (24%), thrombocytopenia (24%), and constipation (22%). Grade 3 treatment-emergent adverse reactions that occurred in more than 3% of patients included neutropenia (16%), peripheral sensory neuropathy (16%), lymphopenia (10%), thrombocytopenia (9%), anemia (7%) and peripheral motor neuropathy (7%). Grade 4 treatment-emergent adverse reactions included neutropenia (9%), thrombocytopenia (5%), fatigue, leukopenia, lymphopenia, pain in extremity, and pain (1 patient, 2% each).

In the pivotal HL and sALCL clinical trials (Studies 1 and 2), 56% of patients experienced peripheral neuropathy. The median time to first onset of any grade was 12 weeks (range, 0.1–41), of Grade 2 was 24 weeks (range, 0.1–52) and of Grade 3 was 33 weeks (range, 6–57). The median time from onset to resolution or improvement of any grade was 16 weeks (range, 1–107), of Grade 2 was 12 weeks (range, 0.7–94), and of Grade 3 was 16 weeks (range, 1–59). Of the patients who reported neuropathy, 56% had complete resolution, 27% had partial improvement, and 17% had no improvement. Of the patients who reported neuropathy, 44% had residual neuropathy at the time of their last evaluation [Grade 1 (27%), Grade 2 (13%), Grade 3 (3%)].

Table 1: Commonly Reported Adverse Reactions (≥ 5% of patients in Study 1 or 2)

	HL **Total N = 102** **n (%) of patients**			**sALCL** **Total N = 58** **n (%) of patients**		
System Organ Class **Preferred Term**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders[a]	*41 (40)*			*22 (38)*		
Leukopenia	62 (61)	6 (6)	-	30 (52)	2 (3)	1 (2)

	HL Total N = 102 n (%) of patients			sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia	55 (54)	15 (15)	6 (6)	37 (64)	9 (16)	5 (9)
Anemia	34 (33)	8 (8)	2 (2)	19 (33)	4 (7)	-
Thrombocytopenia	29 (28)	7 (7)	2 (2)	14 (24)	5 (9)	3 (5)
Lymphopenia	24 (24)	7 (7)	1 (1)	15 (26)	6 (10)	1 (2)
Lymphadenopathy	11 (11)	-	-	6 (10)	-	-
Nervous system disorders	*66 (55)*			*42 (72)*		
Peripheral sensory neuropathy[b]	53 (52)	9 (9)	-	30 (52)	9 (16)	-
Headache	19 (19)	-	-	11 (19)	1 (2)	-
Peripheral motor neuropathy[c]	16 (16)	4 (4)	-	5 (9)	4 (7)	-
Dizziness	11 (11)	-	-	9 (16)	-	-
Memory impairment	1 (1)	-	-	3 (5)	-	-
General disorders and administration site conditions	*72 (71)*			*44 (76)*		
Fatigue	47 (46)	2 (2)	-	22 (38)	2 (3)	1 (2)
Pyrexia	30 (29)	2 (2)	-	20 (34)	1 (2)	-
Chills	13 (13)	-	-	8 (14)	-	-
Pain	7 (7)	-	-	6 (10)	-	1 (2)
Edema peripheral	4 (4)	-	-	8 (14)	-	-
Asthenia	4 (4)	1 (1)	-	5 (9)	-	-
Gastrointestinal disorders	*77 (75)*			*40 (69)*		
Nausea	43 (42)	-	-	23 (40)	1 (2)	-
Diarrhea	37 (36)	1 (1)	-	17 (29)	2 (3)	-
Vomiting	22 (22)	-	-	10 (17)	2 (3)	-
Abdominal pain	17 (17)	1 (1)	1 (1)	5 (9)	1 (2)	-
Constipation	16 (16)	-	-	13 (22)	1 (2)	-
Dyspepsia	5 (5)	-	-	5 (9)	-	-
Abdominal pain upper	6 (6)	1 (1)	-	2 (3)	-	-
Abdominal distension	4 (4)	-	-	3 (5)	-	-
Oral pain	-	-	-	5 (9)	-	-
Gastroesophageal reflux disease	1 (1)	-	-	3 (5)	-	-
Hemorrhoids	1 (1)	-	-	3 (5)	-	-
Infections and infestations	*65 (64)*			*33 (57)*		
Upper respiratory tract infection[d]	48 (47)	-	-	16 (28)	-	-
Bronchitis	9 (9)	-	-	3 (5)	-	-
Urinary tract infection	6 (6)	1 (1)	-	3 (5)	2 (3)	-
Herpes zoster	7 (7)	-	-	1 (2)	-	-

	HL Total N = 102 n (%) of patients			sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Folliculitis	-	-	-	5 (9)	-	-
Respiratory, thoracic and mediastinal disorders	*56 (55)*			*29 (50)*		
Cough	21 (21)	-	-	10 (17)	-	-
Dyspnea	13 (13)	1 (1)	-	11 (19)	1 (2)	-
Oropharyngeal pain	11 (11)	-	-	4 (7)	-	-
Productive cough	6 (6)	-	-	3 (5)	-	-
Nasal congestion	6 (6)	-	-	1 (2)	-	-
Skin and subcutaneous tissue disorders	*64 (63)*			*33 (57)*		
Rash	14 (14)	-	-	14 (24)	-	-
Pruritus	16 (16)	-	-	11 (19)	-	-
Alopecia	13 (13)	-	-	8 (14)	-	-
Night sweats	12 (12)	-	-	4 (7)	-	-
Dry skin	4 (4)	-	-	6 (10)	-	-
Hyperhidrosis	6 (6)	-	-	1 (2)	-	-
Rash pruritic	3 (3)	-	-	4 (7)	-	-
Dermatitis	-	-	-	4 (7)	1 (2)	-
Musculoskeletal and connective tissue disorders	*63 (62)*			*29 (50)*		
Myalgia	17 (17)	-	-	9 (16)	1 (2)	-
Arthralgia	19 (19)	-	-	5 (9)	-	-
Back pain	14 (14)	-	-	5 (9)	1 (2)	-
Pain in extremity	10 (10)	-	-	8 (14)	1 (2)	1 (2)
Muscle spasms	9 (9)	-	-	8 (14)	1 (2)	-
Neck pain	6 (6)	-	-	5 (9)	1 (2)	-
Bone pain	8 (8)	1 (1)	-	2 (3)	-	-
Groin pain	4 (4)	-	-	5 (9)	-	-
Musculoskeletal pain	5 (5)	-	-	4 (7)	1 (2)	-
Psychiatric disorders	*27 (26)*			*16 (28)*		
Insomnia	14 (14)	-	-	9 (16)	-	-
Anxiety	11 (11)	2 (2)	-	4 (7)	-	-
Depression	8 (8)	-	-	4 (7)	1 (2)	-
Confusional state	1 (1)	-	-	3 (5)	1 (2)	-
Metabolism and nutrition disorders	*23 (23)*			*20 (34)*		
Decreased appetite	11 (11)	-	-	9 (16)	1 (2)	-

	HL Total N = 102 n (%) of patients			sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Hyperglycemia	6 (6)	4 (4)	-	3 (5)	1 (2)	-
Hypokalemia	2 (2)	1 (1)	-	5 (9)	2 (3)	-
Dehydration	3 (3)	-	-	3 (5)	1 (2)	-
Hypomagnesemia	2 (2)	-	-	3 (5)	-	-
Investigations	*17 (17)*			*16 (28)*		
Weight decreased	6 (6)	-	-	8 (14)	2 (3)	-
Vascular disorders	*13 (13)*			*8 (14)*		
Hot flush	5 (5)	-	-	3 (5)	-	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*11 (11)*			*9 (16)*		
Hodgkin's disease recurrent	7 (7)	1 (1)	-	-	-	-
Tumor flare	1 (1)	-	-	5 (9)	-	1 (2)
Anaplastic large cell lymphoma t- and null-cell types recurrent	-	-	-	3 (5)	-	-
Cardiac disorders	*5 (5)*			*6 (10)*		
Tachycardia	2 (2)	-	-	3 (5)	-	-
Injury, poisoning and procedural complications	*11 (11)*			*7 (12)*		
Excoriation	-	-	-	3 (5)	-	-

a – includes adverse reactions and laboratory abnormalities

b – includes peripheral sensory neuropathy, paresthesia, neuralgia, hyperesthesia, hypoesthesia, and burning sensation

c – includes peripheral motor neuropathy, demyelinating polyneuropathy, muscular weakness, and polyneuropathy

d – includes terms upper respiratory tract infection, sinusitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, and acute sinusitis

Abnormal Hematologic and Clinical Chemistry Findings in Studies 1 and 2

Please refer to Table 2 for hematologic and clinical chemistry findings.

Laboratory abnormalities

The clinical laboratory parameters for which patients (≥5%) had new or worsening shifts to Grade 3 were low neutrophils (11%), low lymphocytes (10%), low platelets (6%), high glucose (6%), and low leukocytes (5%). New or worsening shifts to Grade 4 occurred for high urate (2%), and low calcium, low lymphocytes, and low hemoglobin (1% each). One patient in the pivotal trials had Grade 3 high ALT and AST.

Table 2: Incidence of New or Worsening ≥Grade 3 Laboratory Abnormalities in Studies 1 and 2

	HL SG035-0003 (N=102) Worst		ALCL SG035-0004 (N=58) Worst		Total Ph 2 (N=160) Worst	
	G3 n (%)	G4 n (%)	G3 n (%)	G4 n (%)	G3 n (%)	G4 n (%)
Hematology						
Hemoglobin (low)	4 (4)	1 (1)	0	0	4 (3)	1 (1)
Leukocytes (low)	6 (6)	0	2 (4)	0	8 (5)	0
Lymphocytes (low)	7 (9)	1 (1)	6 (12)	1 (2)	13 (10)	2 (1)
Neutrophils (low)	12 (12)	0	6 (11)	0	18 (11)	0
Platelets (low)	6 (6)	0	3 (5)	0	9 (6)	0
Biochemistry						
ALT (high)	1 (1)	0	0	0	1 (1)	0
Albumin (low)	1 (1)	0	0	0	1 (1)	0
AST (high)	0	0	1 (2)	0	1 (1)	0
Calcium (low)	1 (1)	0	2 (4)	1 (2)	3 (2)	1 (1)
Glucose (high)	6 (6)	0	3 (5)	0	9 (6)	0
Potassium (low)	2 (2)	0	0	0	2 (1)	0
Sodium (low)	0	0	1 (2)	0	1 (1)	0
Sodium (high)	1 (1)	0	0	0	1 (1)	0
Urate (high)	0	1 (1)	0	2 (4)	0	3 (2)

NOC Adverse Reactions in HL Consolidation Trial (Study 3)

Clinical Trial Adverse Drug Reactions

ADCETRIS was studied in 329 patients with HL at high risk of relapse or progression post-ASCT in a phase 3 randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 ADCETRIS, 160 placebo) received at least one dose of study treatment. In the ADCETRIS-treatment arm, median duration of treatment was 48 weeks (range, 3–60); mean duration of treatment was 38 weeks. In the placebo arm, median duration of treatment was 47 weeks (range, 3–62); mean duration of treatment was 34 weeks. The median number of

treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles (*see Clinical Trials section).*

In the HL consolidation study (Study 3), 67% of ADCETRIS-treated patients experienced any grade of neuropathy. The median time to first onset of any grade was 14 weeks (range, 0.1–47), of Grade 2 was 27 weeks (range, 0.4–52) and of Grade 3 was 34 weeks (range, 7–106). The median time from onset to resolution or improvement of any grade was 23 weeks (range, 0.1–138), of Grade 2 was 24 weeks (range, 1–108) and of Grade 3 was 25 weeks (range, 2–98). Of the patients who reported neuropathy, 59% had complete resolution, 26% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the patients who reported neuropathy, 41% had residual neuropathy at the time of their last evaluation [Grade 1 (28%), Grade 2 (10%), Grade 3 (4%)].

Adverse reactions, regardless of causality, occurring in ≥5% of patients in the ADCETRIS arm and at a higher rate than the placebo arm, regardless of causality, using the NCI CTCAE Version 4.0, are shown in Table 3.

Table 3: Commonly Reported Adverse Reactions (≥5% of patients and at a Higher Rate in the ADCETRIS Arm) in Study 3

	ADCETRIS Total N =167 n (%) of patients			**Placebo Total N = 160 n (%) of patients**		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	148 (89)	51 (31)	20 (12)	89 (56)	14 (9)	10 (6)
Neutropenia[a]	130 (78)	50 (30)	15 (9)	55 (34)	10 (6)	7 (4)
Thrombocytopenia[a]	68 (41)	4 (2)	7 (4)	32 (20)	5 (3)	3 (2)
Anaemia[a]	45 (27)	7 (4)	-	31 (19)	3 (2)	-
Leukopenia	9 (5)	6 (4)	-	3 (2)	1 (1)	-
Nervous system disorders	116 (69)	25 (15)	-	48 (30)	5 (3)	-
Peripheral sensory neuropathy	94 (56)	17 (10)	-	25 (16)	2 (1)	-
Peripheral motor neuropathy	38 (23)	10 (6)	-	3 (2)	1 (1)	-
Headache	19 (11)	3 (2)	-	13 (8)	1 (1)	-
Paraesthesia	16 (10)	3 (2)	-	2 (1)	-	-
Infections and infestations	100 (60)	10 (6)	1 (1)	80 (50)	8 (5)	-
Upper respiratory tract infection	44 (26)	-	-	37 (23)	2 (1)	-
Herpes zoster	12 (7)	1 (1)	-	4 (3)	2 (1)	-
Bronchitis	10 (6)	-	-	10 (6)	-	-
Pneumonia	9 (5)	4 (2)	1 (1)	4 (3)	4 (3)	-
Pharyngitis	8 (5)	-	-	4 (3)	-	-

	ADCETRIS Total N =167 n (%) of patients			Placebo Total N = 160 n (%) of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Gastrointestinal disorders	91 (54)	16 (10)	1 (1)	50 (31)	4 (3)	-
Nausea	36 (22)	5 (3)	-	12 (8)	-	-
Diarrhoea	33 (20)	3 (2)	-	16 (10)	1 (1)	-
Vomiting	27 (16)	4 (2)	-	11 (7)	-	-
Abdominal pain	23 (14)	3 (2)	-	5 (3)	-	-
Constipation	21 (13)	4 (2)	-	5 (3)	-	-
Dyspepsia	11 (7)	-	-	6 (4)	-	-
General disorders and administration site conditions	80 (48)	8 (5)	-	66 (41)	5 (3)	-
Fatigue	40 (24)	3 (2)	-	29 (18)	4 (3)	-
Pyrexia	31 (19)	3 (2)	-	25 (16)	-	-
Chills	17 (10)	-	-	8 (5)	-	-
Asthenia	13 (8)	1 (1)	-	7 (4)	1 (1)	-
Pain	9 (5)	-	-	5 (3)	-	-
Musculoskeletal and connective tissue disorders	75 (45)	2 (1)	-	50 (31)	2 (1)	-
Arthralgia	30 (18)	1 (1)	-	15 (9)	-	-
Muscle spasms	18 (11)	-	-	9 (6)	-	-
Myalgia	18 (11)	1 (1)	-	6 (4)	-	-
Pain in extremity	11 (7)	-	-	8 (5)	-	-
Muscular weakness	8 (5)	-	-	1 (1)	-	-
Respiratory, thoracic and mediastinal disorders	67 (40)	4 (2)	2 (1)	53 (33)	1 (1)	1 (1)
Cough	35 (21)	-	-	26 (16)	-	-
Dyspnoea	21 (13)	-	-	10 (6)	-	1 (1)
Skin and subcutaneous tissue disorders	62 (37)	2 (1)	-	61 (38)	-	-
Pruritus	20 (12)	1 (1)	-	12 (8)	-	-
Rash	13 (8)	1 (1)	-	5 (3)	-	-
Dry skin	10 (6)	-	-	7 (4)	-	-
Investigations	45 (27)	8 (5)	1 (1)	31 (19)	6 (4)	-
Weight decreased	32 (19)	1 (1)	-	9 (6)	-	-
Metabolism and nutrition disorders	40 (24)	10 (6)	1 (1)	20 (13)	4 (3)	1 (1)
Decreased appetite	20 (12)	1 (1)	-	9 (6)	-	-
Hypokalaemia	10 (6)	5 (3)	-	6 (4)	2 (1)	1 (1)
Psychiatric disorders	34 (20)	-	1 (1)	22 (14)	2 (1)	1 (1)
Insomnia	14 (8)	-	-	5 (3)	-	-
Vascular disorders	28 (17)	2 (1)	1 (1)	18 (11)	2 (1)	-
Hypotension	10 (6)	2 (1)	-	4 (3)	1 (1)	-
Cardiac disorders	18 (11)	3 (2)	1 (1)	12 (8)	1 (1)	-
Sinus tachycardia	10 (6)	1 (1)	-	3 (2)	-	-

[a] includes adverse reactions and laboratory abnormalities

Abnormal Hematologic and Clinical Chemistry Findings in Study 3

Please refer to Table 4 for hematologic and clinical chemistry findings.

Laboratory abnormalities

The clinical laboratory parameters for which ADCETRIS-treated patients reported a post-baseline maximum of Grade 3 were low neutrophils (20%), low leukocytes (11%), and low lymphocytes (11%). ADCETRIS-treated patients experienced a post-baseline maximum of Grade 4 for high urate (4%), low neutrophils (2%), low platelets (2%), low calcium (2%), high ALT (1%), high AST (1%), high glucose (1%), and low potassium (1%). Patients on the placebo arm experienced a post-baseline maximum of Grade 4 for low neutrophils (2%), low lymphocytes (1%), low platelets (1%), and high urate (1%).

Table 4: Post-baseline Maximum ≥Grade 3 Laboratory Abnormalities in Study 3

	ADCETRIS Total N =167 Worst		**Placebo Total N = 160 Worst**	
	G3 n (%)	**G4 n (%)**	**G3 n (%)**	**G4 n (%)**
Hematology				
Hemoglobin (low)	1 (1)	-	1 (1)	-
Leukocytes (low)	19 (11)	-	7 (4)	-
Lymphocytes (low)	18 (11)	-	6 (4)	2 (1)
Neutrophils (low)	34 (20)	4 (2)	6 (4)	3 (2)
Platelets (low)	5 (3)	3 (2)	6 (4)	1 (1)
Biochemistry				
ALT (high)	4 (2)	1 (1)	-	-
Albumin (low)	2 (1)	-	-	-
AST (high)	3 (2)	1 (1)	-	-
Bilirubin (high)	1 (1)	-	-	-
Calcium (low)	1 (1)	3 (2)	2 (1)	-
Creatinine (high)	1 (1)	-	-	-
Glucose (high)	4 (2)	1 (1)	1 (1)	-
Glucose (low)	1 (1)	-	-	-
Phosphate (low)	2 (1)	-	3 (2)	-
Potassium (high)	1 (1)	-	-	-
Potassium (low)	4 (2)	2 (1)	3 (2)	-
Sodium (high)	1 (1)	-	-	-
Sodium (low)	2 (1)	-	1 (1)	-

	ADCETRIS Total N =167 Worst		Placebo Total N = 160 Worst	
	G3 n (%)	G4 n (%)	G3 n (%)	G4 n (%)
Urate (high)	-	6 (4)	-	2 (1)

Infusion reactions

NOC/c Two cases of anaphylaxis were reported in phase 1 trials. There were no Grade 3 or 4 infusion-related reactions reported in Studies 1 and 2; however, Grade 1 or 2 infusion-related reactions were reported for 12 HL patients (12%) and 5 sALCL patients (9%). The adverse reactions that were associated with infusion-related reactions in HL patients in Study 1 were chills (5%), nausea (4%), dyspnoea (4%), pruritus (4%), cough (3%), erythema (2%), flushing (2%), throat tightness (2%) and in 1 patient each, dizziness, pyrexia, rash, vomiting, back pain, dyspepsia, dysphagia, hypoaesthesia facial, oropharyngeal pain, and urticaria. The adverse reactions that were associated with infusion-related reactions in sALCL patients in Study 2 were chills, nausea, dizziness, pyrexia, rash, vomiting, diarrhea and local neck swelling each of which occurred in 1 patient.

NOC In Study 3, infusion-related reactions were reported in 25 patients (15%) in the ADCETRIS-treated arm and 3 patients (2%) in the placebo arm. Grade 3 events were reported in 3 of the 25 ADCETRIS-treated patients who experienced infusion-related reactions. No Grade 4 infusion-related reactions were reported. The most common adverse reactions (≥2%) associated with infusion-related reactions reported in ADCETRIS-treated patients were nausea (4%), chills (4%), dyspnea (2%), headache (2%), pruritus (2%), rash (2%), back pain (2%), and vomiting (2%).

Cardiac Adverse Reactions

NOC/c In Study 2, four patients experienced serious cardiac adverse events. Of these, one patient with a history of severe cardiac disease experienced a myocardial infarction while on study therapy. The potential cardiac toxicity of ADCETRIS is unknown, and patients with significant pre-existing cardiac conditions should be monitored closely.

Serious adverse reactions

NOC/c In Study 1, serious adverse reactions, regardless of causality, were reported in 25 (25%) of patients receiving ADCETRIS. In Study 2, serious adverse reactions, regardless of causality, were reported in 25 (43%) of patients receiving ADCETRIS. The serious adverse reactions experienced by 2 HL patients were abdominal pain, pulmonary embolism, demyelinating

polyneuropathy, pneumonitis, pneumothorax, pyelonephritis, and pyrexia. The serious adverse reactions experienced by at least 2 sALCL patients were ALCL recurrent in 3 patients, and septic shock, supraventricular arrhythmia, pain in extremity, and urinary tract infection each in 2 patients.

NOC In Study 3, serious adverse reactions, regardless of causality, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%) and peripheral sensory neuropathy (2%).

Other important serious adverse reactions reported in patients receiving ADCETRIS in other trials included one case of Stevens-Johnson syndrome in an HL patient and one case of tumor lysis syndrome in an sALCL patient.

Dose modifications

NOC/c Adverse reactions that led to dose reductions in at least 2 HL patients in Study1 included peripheral sensory neuropathy (10%). Adverse reactions that led to dose delays in at least 2 HL patients in Study 1 included neutropenia (16%), peripheral sensory neuropathy (13%), thrombocytopenia (4%), upper respiratory tract infection, alanine aminotransferase increased, herpes zoster, influenza, lymphadenopathy and pyelonephritis (2%). Adverse reactions that led to dose reductions in at least 2 sALCL patients in Study 2 included peripheral sensory neuropathy (10%). Adverse reactions that led to dose delays in at least 2 sALCL patients in Study 2 included peripheral sensory neuropathy (14%), neutropenia (12%), and thrombocytopenia (5%).

NOC Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients in Study 3 were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%).

Discontinuations

NOC/c Adverse reactions that led to treatment discontinuation in at least 2 patients with HL in Study 1 were peripheral sensory neuropathy (6%), peripheral motor neuropathy (3%) and Hodgkin's disease recurrent (2%). The adverse reaction that led to treatment discontinuation in patients with sALCL in Study 2 was peripheral sensory neuropathy (12%).

NOC Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients in Study 3. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paraesthesia (1%) and vomiting (1%).

Deaths

NOC/c In the HL pivotal trial (Study 1), there were no deaths within 30 days of the last study treatment. In the sALCL pivotal trial Study 2), 6 deaths occurred within 30 days of the last study treatment and were due to ALCL recurrent (3 patients), acute myocardial infarction and acute renal failure not related to disease (both in 1 patient), respiratory failure secondary to progressive sALCL (1 patient) and sudden death (1 patient).

NOC In the HL consolidation trial (Study 3), one patient in the ADCETRIS arm died within 30 days of last study treatment due to treatment-related ARDS associated with pneumonitis.

Beyond 30 days after last study treatment, one ADCETRIS-treated patient died 40 days after last study treatment due to ARDS considered not treatment-related and after a prior episode of treatment-related acute pancreatitis; and one ADCETRIS-treated patient died 706 days after last study treatment due to myelodysplastic syndrome considered treatment related.

Immunogenicity

NOC/c Patients with HL and sALCL in Studies 1 and 2 *(see Clinical Trials section)* were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Seven percent (7%) of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 27% of patients developed transiently positive antibodies (positive test at one or two timepoints). One additional patient who tested positive at baseline had persistently positive antibodies. Two patients with persistently positive antibodies experienced adverse events consistent with infusion reactions that led to discontinuation of treatment.

Of 59 patients with ATA-positive samples, 31% were negative for the presence of neutralizing antibodies, 63% had at least one sample that was positive for the presence of neutralizing antibodies, and the remainder were of unknown status.

A higher incidence of infusion-related reactions was associated with patients who had positive antibodies compared to those who tested transiently positive or negative. The presence of antibodies to brentuximab vedotin did not correlate with a substantial reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin.

Less Common Clinical Trial Adverse Drug Reactions (<5%, all grades)

The following adverse reactions, regardless of relationship to ADCETRIS, were reported in <5% of patients treated with ADCETRIS in either the relapsed/refractory HL or sALCL pivotal trial (Studies 1 and 2) or in ADCETRIS-treated patients at a rate of <5% and at a rate ≥1% higher

than placebo in the HL consolidation trial (Study 3). These reactions are presented in alphabetical order.

Blood and lymphatic system disorders: anemia of chronic disease, coagulopathy, eosinophilia, febrile neutropenia, haemolysis, idiopathic thrombocytopenic purpura, lymph node pain, lymphopenia, macrocytosis, spenomegaly

Cardiac disorders: acute myocardial infarction, angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block complete, bradycardia, cardiac failure congestive, cyanosis, left ventricular dysfunction, left ventricular hypertrophy, myocardial infarction, supraventricular tachycardia

Congenital, familial and genetic disorders: trisomy 21

Ear and labyrinth disorders: deafness, deafness unilateral, ear congestion, ear discomfort, ear pain, ear pruritus, middle ear effusion, otorrhoea, tinnitus, vertigo, vestibular disorder

Endocrine disorders: Addison's disease, hypogonadism, hypothyroidism**,** secondary adrenocortical insufficiency

Eye disorders: astigmatism, blepharospasm, cataract, conjunctival hyperemia, diabetic retinopathy, diplopia, dry eye, eye discharge, eye pain, eye pruritus, glare, lacrimal disorder, lacrimation increased, ocular hyperemia, photophobia, photopsia, retinal vascular disorder, retinal vein occlusion, visual acuity reduced, vision blurred, visual impairment

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal hernia, abdominal pain lower, abdominal pain upper, abdominal tenderness, ascites, Barrett's esophagus, cheilitis, colitis, dental caries, dry mouth, dysphagia, epigastric discomfort, erosive duodenitis, fecal incontinence, flatulence, gastritis, gastroduodenitis, gastrotestinal disorder, gastrointestinal hemorrhage, gastrointestinal inflammation, gastrointestinal pain, gastrointestinal ulcer, gingival bleeding, hematemesis, hematochezia, hemorrhoidal hemorrhage, hiatus hernia, ileus, impaired gastric emptying, intestinal perforation, lip exfoliation, loose tooth, mouth ulceration, odynophagia, oesophageal pain, oesophageal spasm, oesophageal stenosis, oral disorder, pancreatitis acute, proctalgia, rectal hemorrhage, rectal tenesmus, retching,sensitivity of teeth, stomatitis, tongue discoloration, tooth discoloration, toothache, umbilical hernia

General disorders and administration site conditions: axillary pain, catheter site inflammation, catheter site pain, catheter site related reaction, chest discomfort, chest pain, cyst, disease progression, oedema, face oedema, feeling cold, feeling hot, fibrosis, gait disturbance, generalised oedema, influenza like illness, infusion site erythema, local swelling, malaise,

mucosal inflammation, non-cardiac chest pain, oedema, peripheral swelling, sudden death, temperature intolerance, tenderness, ulcer

Hepatobiliary disorders: hepatic mass, hepatic steatosis, hepatomegaly, hepatotoxicity

Immune system disorders: allergy to arthropod bite, contrast media allergy, drug hypersensitivity, hypersensitivity, hypogammaglobulinaemia, seasonal allergy

Infections and infestations: abscess, acute hepatitis B, acute sinusitis, acute tonsillitis, appendicitis, atypical pneumonia, bronchopulmonary aspergillosis, candidiasis, catheter site cellulitis, cellulitis, chronic hepatitis B, conjunctivitis, conjunctivitis infective, cystitis, cystitis Escherichia, diverticulitis, ear infection, endocarditis staphylococcal, external ear cellulitis, fungal infection, fungal skin infection, furuncle, gastroenteritis, gastroenteritis viral, gastrointestinal infection, gingival abscess, groin abscess, h1n1 influenza, hepatic candidiasis, herpes simplex, herpes virus infection, hordeolum, impetigo, infection, influenza, klebsiella bacteremia, laryngitis, lower respiratory tract infection fungal, myelitis, oesophageal infection, oral candidiasis, oral herpes, otitis externa, paronychia, pneumocystis jiroveci pneumonia, pneumonia, pneumonia staphylococcal, pyelonephritis, scrotal infection, septic shock, soft tissue infection, staphylococcal bacteremia, staphylococcal skin infection, superinfection bacterial, tinea infection, tonsillitis, tonsillitis bacterial, tooth infection, tracheitis, urinary tract infection enterococcal, urinary tract infection staphylococcal, viral infection, viral pharyngitis, viral upper respiratory tract infection

Injury, poisoning and procedural complications: animal bite, ankle fracture, arthropod bite, contusion, foot fracture, joint sprain, ligament sprain, lower limb fracture, muscle strain, open wound, procedural pain, radiation injury, radiation pneumonitis, rib fracture, thermal burn, wrist fracture, wound

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, biopsy bronchus, biopsy liver, blood alkaline phosphatase increased, blood cholesterol increased, blood creatinine increased, blood creatinine phosphokinase increased, blood triglycerides increased, blood uric acid increased, body temperature increased, c-reactive protein increased, cardiac murmur, ejection fraction decreased, gallop rhythm present, human papilloma virus test positive, international normalized ratio increased, liver function test abnormal, nerve conduction studies abnormal, respiratory rate increased, scan abdomen abnormal, staphylococcus test positive, transaminases increased, weight increased

Metabolism and nutrition disorders: diabetes mellitus, fluid overload, folate deficiency, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperuricemia,

hypoalbuminemia, hypocalcemia, hypoglycemia, hyponatremia, hypophagia, hypophosphatemia, polydipsia, tumor lysis syndrome, type 2 diabetes mellitus, vitamin D deficiency

Musculoskeletal and connective tissue disorders: amyotrophy, arthritis, arthropathy, exostosis, flank pain, joint effusion, joint hyperextension, joint stiffness, joint swelling, limb discomfort, muscle twitching, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myositis, periarthritis, sensation of heaviness, spinal disorder, synovial cyst, tendonitis

Neoplasms benign, malignant and unspecified (including cysts and polyps): bladder cancer, colon adenoma, diffuse large b-cell lymphoma, lung neoplasm malignant, malignant pleural effusion, mycosis fungoides, myelodysplastic syndrome, pancreatic carcinoma, urethral papilloma

Nervous system disorders: ageusia, amnesia, ataxia, balance disorder, basilar migraine, burning sensation, carpal tunnel syndrome, cognitive disorder, convulsion, decreased vibratory sense, diabetic coma, dysgeusia, dyspraxia, encephalopathy, facial palsy, hemorrhage intracranial, hyperesthesia, hyporeflexia, Lhermitte's sign, lethargy, lumbar radiculopathy, migraine, migraine with aura, nerve compression, Parkinson's disease, parosmia, peroneal nerve palsy, polyneuropathy, post herpetic neuralgia, presyncope, restless leg syndrome, retinal migraine, sensory disturbance, sinus headache, somnolence, spinal cord compression, syncope, tremor, tunnel vision

Psychiatric disorders: agitation, anger, anticipatory anxiety, depressed mood, libido decreased, mental status changes, mood swings, panic attack, restlessness, sleep disorder, suicidal ideation

Renal and urinary disorders: chromaturia, diabetic nephropathy, dysuria,haematuria, hydronephrosis, micturition disorder, nephrolithiasis, pollakiuria, renal cyst, renal failure, renal failure acute, urinary hesitation, urinary incontinence

Reproductive system and breast disorders: amenorrhea, artificial menopause, breast mass, breast tenderness, dysmenorrhea, erectile dysfunction, menometrorrhagia, menopausal symptoms, menorrhagia, menstruation irregular, ovarian cyst, pelvic pain, penile swelling, scrotal swelling, vaginal hemorrhage, vulvovaginal dryness

Respiratory, thoracic and mediastinal disorders: allergic cough, asthma exercise induced, atelectasis, bronchial hyperreactivity, bronchospasm, dysphonia, dyspnea exertional, emphysema, epistaxis, hiccups, hemoptysis, hyperventilation, hypoxia, increased upper airway secretion, laryngeal edema, lung consolidation, lung disorder, nasal discomfort, paranasal cyst, paranasal sinus hypersecretion, pharyngeal oedema, pleural effusion, pleuritic pain, pneumonitis, pneumothorax, postnasal drip, productive cough, pulmonary fibrosis, pulmonary edema, pulmonary embolism, pulmonary toxicity, respiratory failure, respiratory tract congestion,

rhinorrhoea, rhinitis allergic, sinus congestion, sinus disorder, throat irritation, tonsillar disorder, tonsillar hypertrophy, throat tightness, tonsillar inflammation, tracheal disorder, tracheal pain, wheezing

Skin and subcutaneous tissue disorders: acne, dapsone syndrome, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis contact, dermatitis exfoliative, ecchymosis, eczema, erythema, exfoliative rash, hypoesthesia facial, nail disorder, nail ridging, onychoclasis, onychomadesis, periorbital edema, pruritus generalized, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, scar, skin discoloration, skin exfoliation, skin lesion, skin nodule, Stevens-Johnson syndrome, telangiectasia, urticaria, yellow skin

Surgical and medical procedures: cataract operation

Vascular disorders: deep vein thrombosis, flushing, hypertension, hypotension, orthostatic hypotension, peripheral artery aneurysm, Raynaud's phenomenon, thrombophlebitis

Additional Clinical Trial Experience in HL and sALCL

Limited studies have investigated retreatment (N=29) and extended treatment (N=19) with ADCETRIS 1.8 mg/kg intravenously every 3 weeks in patients with HL or sALCL. Median duration of retreatment was 23 weeks (range, 6 to 167 weeks) and the median number of cycles was 7 (range, 2 to 37 cycles). Median duration of extended treatment was 90 weeks (range, 59 to 139 weeks) and the median number of cycles was 24 (range, 17 to 42 cycles). In these studies, the types of adverse events observed were similar to those observed in the phase 2 clinical trials.

Among retreated HL (n=21) and sALCL (n=8) patients, the incidences of peripheral motor neuropathy (HL: 29%, sALCL: 25%) were increased compared to the incidences observed in the phase 2 trials.

Extended treatment of patients with HL (n=13) or sALCL (n=6) was associated with higher incidences of peripheral sensory neuropathy (HL: 77%, sALCL: 67%), peripheral motor neuropathy (HL: 23%, sALCL 17%) and upper respiratory tract infections (HL: 62%, sALCL: 67%) when compared to the incidences of these events in the phase 2 trials.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: Pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain.

Hepatobiliary disorders: Hepatotoxicity, including fatal outcome (*see Warnings and Precautions section*).

Infections and infestations: Progressive Multifocal Leukoencephalopathy (PML) has been reported in patients receiving ADCETRIS *(see Warnings and Precautions section)*.

Respiratory, thoracic and mediastinal disorders: Pulmonary toxicity *(see Warnings and Precautions section)*.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN), including fatal outcomes (*see Warnings and Precautions section*).

DRUG INTERACTIONS

Overview

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. In vitro data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

Drug-Drug Interactions

Bleomycin: Co-administration of bleomycin with ADCETRIS is associated with pulmonary toxicity.

CYP3A4 and P-gp Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A (*see Action and Clinical Pharmacology section)*. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 and P-gp inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 and P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions. Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations (*see Action and Clinical Pharmacology section)*. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

Drug-Food Interactions

Grapefruit has CYP3A4 inhibitory activity. Therefore, ingestion of grapefruit while on ADCETRIS therapy may increase MMAE plasma concentrations. Patients receiving concomitant administration of ADCETRIS with grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits that are known to inhibit CYP3A4 should be closely monitored for adverse reactions.

Drug-Herb Interactions

No drug-herb interactions have been established.

Drug-Laboratory Interactions

No drug-laboratory interactions have been established.

Drug-Lifestyle Interactions

No drug-lifestyle interactions have been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ADCETRIS is for intravenous infusion and must be reconstituted and diluted prior to administration. **Do not administer as an intravenous push or bolus.**

Dosing modification may be needed in the following situations;

- **Peripheral Neuropathy:** For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.
- **Neutropenia:** The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg may be considered.
- **Thrombocytopenia:** If Grade 3 or 4 thrombocytopenia develops, monitor closely and consider platelet transfusions or dose delays.

- **Severe renal insufficiency:** Avoid use in patients with severe renal impairment (creatinine clearance <30 mL/min).
- **Hepatic insufficiency:** The starting dose should be 1.2 mg/kg for patients with mild hepatic impairment (Child-Pugh A). Closely monitor these patients for adverse reactions. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

Recommended Dose and Dosage Adjustment

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

The recommended starting dose in patients with mild hepatic impairment (Child-Pugh A) is 1.2 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks (*see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency*).

The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

For relapsed/refractory HL and sALCL, continue treatment until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, patients who achieve stable disease or better should continue to receive ADCETRIS for a minimum of 8 cycles and up to a maximum of 16 cycles. Treatment beyond 16 cycles should be administered only when agreed to by the patient and their health care professional after consideration of the risks associated with prolonged treatment.

For HL consolidation treatment, initiate ADCETRIS treatment within 4–6 weeks post-ASCT or upon recovery from ASCT. These patients should continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

Do not administer as an intravenous push or bolus.

Missed Dose

A missed dose should be administered as soon as possible. Subsequent doses should not be administered less than 3 weeks apart.

Administration

Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

Reconstitution:
Calculate the dose (mg) and number of vials of ADCETRIS required. The dose for patients with a weight of >100 kg should be calculated based on a weight of 100 kg. Reconstitute each 50 mg vial of ADCETRIS with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin. Direct the stream toward wall of vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. **DO NOT SHAKE**. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates. Following reconstitution, dilute immediately into an infusion bag, or store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.** Discard any unused portion left in the vial.

Dilution:
Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed and withdraw this amount from the vials. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100 mL to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin. ADCETRIS can be diluted into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection. Gently invert the bag to mix the solution. ADCETRIS contains no bacteriostatic preservatives. Following dilution, infuse the ADCETRIS solution immediately, or store the solution at 2–8°C and use within 24 hours of reconstitution. **DO NOT FREEZE.**

Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.

OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

For management of a suspected drug overdose, contact your regional Poison Control Center.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Brentuximab vedotin is an ADC (antibody-drug conjugate). The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a potent microtubule disrupting agent.

MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells. MMAE release by CD30-independent mechanisms and contributions to the mechanism of action by other antibody-associated functions have not been excluded.

Pharmacodynamics

Electrocardiography

Administration of brentuximab vedotin did not prolong the QTc interval from baseline, however, small increases in QTc interval cannot be excluded because of study limitations. The ECG study also showed a brentuximab vedotin-associated decrease from baseline in the QTc interval (maximum mean decrease from baseline approximately 7 ms [90% CI: 3.5, 11.2]). The clinical significance of this finding is unknown.

Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 trials and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a PK profile similar to that of the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

Table 5: Pharmacokinetic Parameters for ADC and MMAE

	Dose (mg/kg)	**N**	**$AUC_{0\text{-}21d}$ (day·µg/mL)**	**C_{max} (µg/mL)**	**$t_{1/2}$ (day)**	**CL (L/day)**	**V_{ss} (L)**
ADC	1.2	4	45.21 (63)	18.89 (27)	3.79 (11)	1.96 (105)	5.85 (260)
	1.8	12	76.65 (31)	31.98 (29)	4.43 (38)	1.76 (17)	8.21 (24)
	Dose* (mg/kg)	**N**	**$AUC_{0\text{-}21d}$ (day·ng/mL)**	**C_{max} (ng/mL)**	**$t_{1/2}$ (day)**		
MMAE	1.2	4	20.05 (215)	2.72 (272)	3.13 (28)		
	1.8	12	36.07 (47)	4.97 (43)	3.60 (25)		

Data are based on non-compartmental analysis of data obtained in study SG035-0001 (the phase I dose-escalation study) and all PK parameters are summarized by the geometric mean (% CV).
* Dose of brentuximab vedotin.

Absorption:

Maximum concentrations of ADC were typically observed close 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 from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of ADCETRIS, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of ADCETRIS. MMAE exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution:
In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

In humans, the mean steady state volume of distribution was approximately 6–10 L for ADC. The typical apparent volume of distribution for MMAE, an estimate based on population PK modeling, was 44 L. The organ distribution of MMAE in humans is unknown. In rats, MMAE was rapidly distributed through the body (*see Nonclinical Pharmacokinetics section*).

Metabolism:
In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. 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 CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Intact MMAE was the primary species excreted in humans, suggesting a low propensity for metabolism based biotransformations. MMAE was excreted in both feces (72%) and urine (28%) in patients with CD30-positive hematologic malignancies, though mass balance was not achieved with approximately 23.5% of the equivalent amount of MMAE administered being recovered in excreta. A metabolite not previously observed was detected in humans in both feces and urine, but this metabolite was a combination of two biotransformations that were observed in humans.

Elimination:
MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during an ADCETRIS infusion was recovered in both urine and

feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

Special Populations and Conditions:

Gender:
Based on the population PK analysis, gender was found to be a covariate in the population PK. The ADC volume of distribution in female patients was 14% lower than male patients.

Pediatric patients:
The safety and efficacy in children aged less than 18 years have not been established.

Geriatric patients:
The safety and efficacy in elderly patients aged 65 and older have not been established.

Hepatic insufficiency:
The liver is a route of clearance for MMAE. A study evaluated the pharmacokinetics 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 in patients with hepatic impairment.

Renal insufficiency:
The kidney is a route of excretion for MMAE. A study evaluated the pharmacokinetics 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 in patients with severe renal impairment (creatinine clearance <30 mL/min).

STORAGE AND STABILITY

Store vial at 2–8°C in the original carton to protect from light.

SPECIAL HANDLING INSTRUCTIONS

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ADCETRIS (brentuximab vedotin) for Injection is supplied as a single-use vial containing 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder. Prior to administration, the contents of the ADCETRIS vial are reconstituted with 10.5 mL of Sterile Water for Injection, USP resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL brentuximab vedotin. The pH of the reconstituted solution is approximately 6.6. Non-medicinal ingredients include sodium citrate dihydrate, citric acid monohydrate, trehalose dihydrate and polysorbate 80.

PART II: SCIENTIFIC INFORMATION

ADCETRIS has been issued conditional marketing authorization for:

- the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates
- the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen

These marketing authorizations are conditional, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

ADCETRIS has been issued non-conditional marketing authorization for:

- the post-ASCT consolidation treatment of patients with HL at increased risk* of relapse or progression.

**See Part II, Clinical Trials*

PHARMACEUTICAL INFORMATION

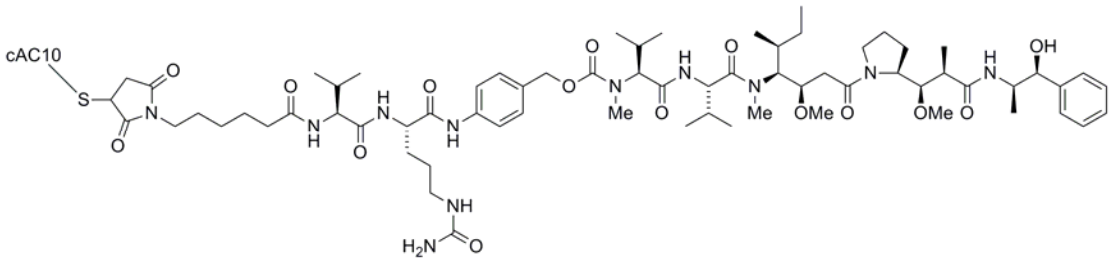
Drug Substance

Proper name: Brentuximab vedotin

Chemical name: Chimeric IgG_1 cAC10 covalently linked to vcMMAE

Molecular formula and molecular mass: $C_{6860}H_{10532}N_{1740}O_{2168}S_{40}$
Average mass: 153,352 Da

Structural formula:



Physicochemical properties:
The brentuximab vedotin bulk drug substance is colorless and slightly opalescent.
Average drug-to-antibody molar ratio (MRD): 4

Product Characteristics

Brentuximab vedotin is an ADC (antibody-drug conjugate) composed of a CD30-directed monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the potent antimitotic small molecule monomethyl auristatin E (MMAE). cAC10 is produced by Chinese hamster ovary cell culture. The small molecule, MMAE, attached to an enzyme-cleavable linker (maleimidolcaproyl-valine-citrulline-p-aminobenzyloxycarbonyl-MMAE, vcMMAE) is produced by chemical synthesis. Brentuximab vedotin is produced via the chemical conjugation of cAC10 to vcMMAE.

CLINICAL TRIALS

Hodgkin Lymphoma

NOC/c ***Pivotal Phase 2 Clinical Trial in Relapsed/Refractory HL (Study 1)***

Study demographics and trial design

The efficacy of ADCETRIS in patients with relapsed or refractory HL was evaluated in one pivotal open-label, single-arm, multicenter study. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks for up to 16 cycles. An independent review facility (IRF) performed efficacy evaluations, including overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response, which were assessed using clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma.

NOC/c Table 6: Summary of Baseline Patient and Disease Characteristics in Study 1

	HL
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 (range)	3.5 (1-13)
Disease characteristics	
Relapsed	59 (58%)
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 disease is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

Study results

The efficacy results for Study 1 are summarized in Table 7. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 7: Efficacy Results in Patients with Hodgkin Lymphoma (Study 1)

	N=102		
	Percent (95% CI)	Duration of Response, in months	
		Median (95% CI)	Range
Overall response rate (ORR)	75 (65, 83)	6.7 (3.6, 14.8)	1.2+ to 26.1+
Complete remission (CR)	32 (23, 42)	Not reached (12.08, NE*)	1.4 to 26.1+
Partial remission (PR)	42 (32, 52)	3.5 (2.2, 4.1)	1.2+ to 21.9+

*Not estimable

+ Follow up was ongoing at the time of data submission.

Retreatment with ADCETRIS

The efficacy of retreatment in patients who had previously responded to ADCETRIS was evaluated in one phase 2, open-label, multicenter trial. Retreatment with ADCETRIS was evaluated in 29 patients (21 with relapsed HL and 8 with relapsed sALCL). Twenty-seven patients received a starting dose of 1.8 mg/kg and two patients received a starting dose of

1.2 mg/kg (one patient each with HL and sALCL) administered intravenously over 30 minutes every 3 weeks.

Of the 20 evaluable patients with relapsed HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with ADCETRIS retreatment, for an ORR of 60%.

NOC ***Randomized Phase 3 Placebo-controlled Clinical Trial in HL Consolidation (Study 3)***

Study demographics and trial design

The efficacy of ADCETRIS in patients with HL at high risk of relapse or disease progression post-ASCT was studied in one phase 3 randomized, double-blind, placebo-controlled clinical trial. Three hundred twenty-nine patients were randomized 1:1 to receive placebo or ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles, beginning 30–45 days post-ASCT. Randomization was stratified by response status following frontline therapy and to most recent pre-ASCT salvage therapy. Patients in the placebo arm with progressive disease (PD) per investigator could receive ADCETRIS as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by IRF. Clinical lymphoma assessments were done at every cycle during treatment, every 3 months in follow up until 24 months, and then every 6 months until disease progression or study closure.

Subjects were enrolled based on meeting at least one of the three criteria used to define high risk of post-ASCT relapse or progression: refractory to frontline therapy, relapsed <12 months following frontline therapy, or relapsed >12 months with extranodal involvement. Patients were required to have obtained a CR, PR, or stable disease (SD) to most recent pre-ASCT salvage therapy.

The majority of the study population were refractory or relapsed <12 months to frontline therapy and had 1 or more other risk factors, including B symptoms following frontline therapy, extranodal disease, 2 or more prior salvage therapies, or response of PR or SD to most recent pre-ASCT salvage therapy.

NOC Table 8: Summary of Baseline Patient and Disease Characteristics in Study 3

Patient characteristics	ADCETRIS N = 165	Placebo N = 164
Median age, (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[a]	1 (1%)	0 (0%)
Number of prior systemic salvage therapies		
1	94 (57%)	86 (52%)
≥2 (range, 2-7)	71 (43%)	79 (48%)
Disease characteristics		
HL status after frontline therapy[b]		
Refractory	99 (60%)	97 (59%)
Relapse < 12 months	53 (32%)	54 (33%)
Relapse ≥ 12months with extranodal involvement	13 (8%)	13 (8%)
Best response to salvage therapy pre-ASCT[c]		
CR	61 (37%)	62 (38%)
PR	57 (35%)	56 (34%)
SD	47 (28%)	46 (28%)
Extranodal involvement at pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms following frontline therapy	47 (28%)	40 (24%)

[a] Patient had an ECOG status of 1 at randomization, which worsened to a status of 2 prior to the first dose of study treatment
[b] Refractory/relapsed status at the end of frontline treatment with standard chemotherapy or a combined modality
[c] Per the Revised Response Criteria for Malignant Lymphoma (2007)

Study results

The efficacy results are summarized in Table9. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the ADCETRIS arm compared with the placebo arm.

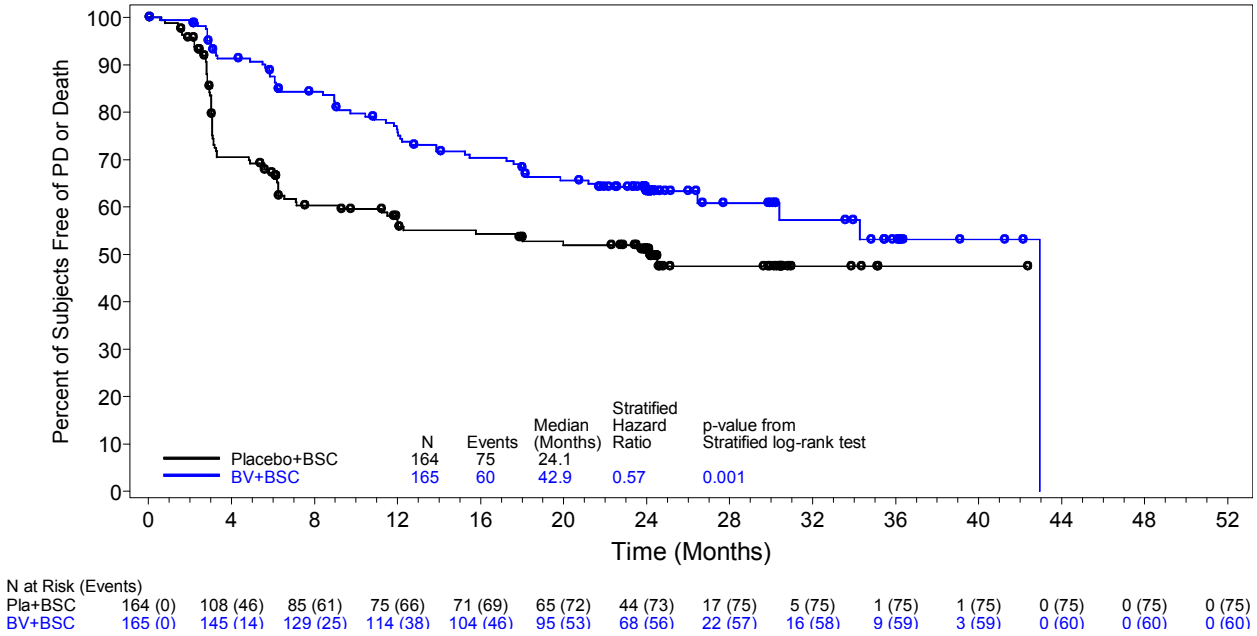
An interim OS analysis conducted after an observation of 30 months (range, 0–50) demonstrated 53 patients (16%) had died: 28/165 patients (17%) in the ADCETRIS arm versus 25/164 patients (15%) in the placebo arm. Interpretation of the interim OS data is limited by the small number of events observed within a relatively short follow-up period and the high rate of crossover to ADCETRIS in the placebo arm (72/136 patients who received subsequent therapy).

Table 9: Efficacy Results in Patients with HL Consolidation (Study 3)

Progression-free Survival per IRF	ADCETRIS N=165	Placebo N=164
Number of events (%)	60 (36)	75 (46)
Median months (95% CI)	42.9[a] (30.4, 42.9[a])	24.1 (11.5, NE[b])
Stratified Hazard Ratio[c] (95% CI)	0.57 (0.40, 0.81)	
Stratified Log-Rank Test p-value[d]	0.001	

[a] Estimates are unreliable
[b] Not estimable
[c] Comparing ADCETRIS to placebo. HR <1.0 based on stratified Cox PH model adjusting for status following frontline therapy and best clinical response to most recent pre-ASCT salvage therapy
[d] Computed using stratification factors (see footnote c)

Figure 1: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 3)



BV: Brentuximab Vedotin; BSC: Best Supportive Care

Post-hoc exploratory analyses were performed to evaluate the potential association between the number of risk factors present at baseline and PFS. In the analyses of PFS per IRF stratified by number of risk factors present at baseline, the proportion of patients with ≥ 2 risk factors and disease progression or death was 36.1% (52/144) in the ADCETRIS arm and 50% (68/136) in the placebo arm. The corresponding proportions for patients with 1 risk factor were 42.9% (9/21) in the ADCETRIS arm and 28.6% (8/28) in the placebo arm. These results should be interpreted with caution given the inherent limitations associated with post-hoc exploratory sub-group analysis.

Systemic Anaplastic Large Cell Lymphoma

NOC/c *Pivotal Phase 2 Clinical Trial in Relapsed/Refractory sALCL (Study 2)*

Study demographics and trial design

The efficacy of ADCETRIS in patients with relapsed or refractory sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed or refractory after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks for up to 16 cycles. An independent review facility performed efficacy evaluations, including overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response, which were assessed using clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma.

Table 10: Summary of Baseline Patient and Disease Characteristics in Study 2

	sALCL
Patient characteristics	**N = 58**
Median age, yrs (range)	52 years (14-76)
Gender	33M (57%)/25F (43%)
ECOG status	
0	19 (33%)
1	38 (66%)
Prior ASCT	15 (26%)
Prior chemotherapy regimens (range)	2 (1-6)
Disease characteristics	
Relapsed	29 (50%)
Primary Refractory to frontline therapy[a]	36 (62%)
Refractory to most recent therapy	29 (50%)
ALK[b]-negative	42 (72%)
Baseline B symptoms	17 (29%)
Stage III at initial diagnosis	8 (14%)
Stage IV at initial diagnosis	21 (36%)

a - Primary refractory disease is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.
b – anaplastic lymphoma kinase

Study results

The efficacy results for Study 2 are summarized in Table 11. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 11: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma (Study 2)

	N=58		
	Percent (95% CI)	Duration of Response, in months	
		Median (95% CI)	Range
Overall response rate (ORR)	86 (75, 94)	13.2 (5.7, NE*)	0.1 to 21.7+
Complete remission (CR)	59 (45, 71)	Not reached (13.0, NE*)	0.7 to 21.7+
Partial remission (PR)	28 (17, 41)	2.0 (1.3, 3.0)	0.1 to 21+

*Not estimable

+ Follow up was ongoing at the time of data submission

Retreatment with ADCETRIS

The efficacy of retreatment in patients who had previously responded to ADCETRIS was evaluated in one phase 2, open-label, multicenter trial. Retreatment with ADCETRIS was evaluated in 29 patients (21 with relapsed HL and 8 with relapsed sALCL). Twenty-seven patients received a starting dose of 1.8 mg/kg and two patients received a starting dose of 1.2 mg/kg (one patient each with HL and sALCL) administered intravenously over 30 minutes every 3 weeks.

Of the 8 sALCL patients, 3 were retreated twice for a total of 11 retreatment experiences. Retreatment with ADCETRIS resulted in 6 CRs (55%) and 4 PRs (36%), for an ORR of 91%.

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics

The serum pharmacokinetics of ADC following an intravenous dose of brentuximab vedotin in patients with CD30-positive hematologic malignancies were similar to other antibody products. Maximum concentrations were typically observed at the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days at the 1.8 mg/kg dose level. Exposures were approximately dose proportional. After multiple-dose administration of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation was observed with multiple doses at the q3wk schedule.

The plasma pharmacokinetics of MMAE following an intravenous dose of brentuximab vedotin in patients with CD30-positive hematologic malignancies appeared to be formation-limited. Maximum concentrations were typically observed 2 days postdose and MMAE declined with an apparent terminal half-life of approximately 4 days at the 1.8 mg/kg dose level. Exposures were approximately dose proportional. MMAE $AUC_{0\text{-}21d}$ and C_{max} decreased following multiple doses.

Following an intravenous dose of brentuximab vedotin (1.2 to 2.7 mg/kg), the steady-state volume of distribution for ADC was approximately 6–10 L, indicating that ADC was primarily limited to the vascular space. Based on the population pharmacokinetic model, the typical apparent volume of distribution for MMAE was 44 L.

Nonclinical Pharmacokinetics

In rats, MMAE was rapidly and widely distributed. Tissues with levels of MMAE 10-fold higher than in plasma include (AUC ratio): anterior pituitary gland (111), bone marrow (52), posterior pituitary gland (48), thyroid (41), small intestine (40), thymus (39), spleen (36), lung (33), lymph node (31), cecum (27), uveal tract of the eye (25), large intestine (21), salivary gland (21), choroid plexus (20), kidney cortex (20), kidney medulla (19), adrenal gland (18), heart (17), brown adipose tissue (14), Harderian gland (14), urinary bladder (13), stomach (12), liver (12), and pancreas (12). MMAE levels in the brain and spinal cord were below the limit of quantitation. The half-life of MMAE in the thymus (3 d), pituitary glands (0.7–1 d), and eye uveal tract (24 d) was longer than the half-life in plasma (0.7 d).

Active metabolites of MMAE, present at concentrations less than 10% of MMAE, have been measured in the excreta of rats and humans. The circulating levels and clinical significance of these metabolites are unknown.

Nonclinical Pharmacology

The nonclinical pharmacology program of ADCETRIS evaluated safety, pharmacokinetics, toxicology and the ability of brentuximab vedotin to kill CD30-positive cells in vitro and in vivo as well as the ability to inhibit tumor progression in rodent models of experimental cancer.

Primary Pharmacodynamics

Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells. MMAE release by CD30-independent mechanisms and contributions to the mechanism of action by other antibody-associated functions have not been excluded.

In vitro

The primary pharmacodynamic effect of brentuximab vedotin, cell death, is the result of a multi-step process involving: CD30 binding, internalization, trafficking to lysosomes, release of MMAE, binding to tubulin, cell cycle arrest, and apoptosis. Brentuximab vedotin binds to CD30-

positive cells (ALCL cell line Karpas 299) at a dissociation constant (KD) of approximately 2 nM. Cell surface localization and intracellular localization of the ADC were demonstrated by fluorescence microscopy after binding to CD30-positive cells (HL cell line L540cy). Within 4 hours of incubation at 37°C, ADC was detected inside cells and co-localized with intracellular lysosomes indicating internalization and trafficking to lysosomes. Monomethyl auristatin E was released from brentuximab vedotin intracellularly in CD30-positive human HL (L540cy and L428) and ALCL (Karpas 299) cell lines. Free MMAE inhibited microtubule polymerization in vitro, and tumor cells (CD30-positive embryonal carcinoma Tera-2 cells) treated with MMAE or brentuximab vedotin displayed a rounded morphology and disrupted micotubule network. In vitro, brentuximab vedotin arrested cells in the G2/M phase of the cell cycle in an antigen-dependent manner.

In vitro cytotoxicity studies showed that brentuximab vedotin selectively killed CD30-positive HL and ALCL cell lines (IC_{50} of 0.091 and 0.032 nM, respectively), but not CD30-negative cells (WSU-NHL) at concentrations of 6.7 nM. In contrast to the CD30-specific cytotoxicity of brentuximab vedotin, MMAE killed both the CD30-positive and CD30-negative cells at low nM concentrations, demonstrating the antigen specificity conferred by the antibody to the ADC.

In vivo

In vivo, the cytotoxic effect of brentuximab vedotin was demonstrated as antitumor activity in xenograft models derived from human HL and ALCL tumor cell lines. Tumor growth was delayed when mice were treated with 1 mg/kg brentuximab vedotin every 4 days for a total of 4 doses (q4d x 4) in the HL L428 and L540cy subcutaneous tumor xenograft models. Furthermore, treatment with brentuximab vedotin at 2 mg/kg q4d x 3 and 3 mg/kg q4d x 4, resulted in durable responses with no measurable tumor mass at the end of the study in the L428 and L540cy models, respectively. In contrast, treatment in mice with non-binding control ADC did not result in any durable responses. Likewise, administration of MMAE to tumor bearing mice, at doses 5-fold higher than that delivered by brentuximab vedotin, induced minimal tumor growth delay and no complete or durable responses.

In ALCL xenograft disseminated and subcutaneous models, a survival advantage and dose-dependent durable responses, respectively, were also observed in mice treated with brentuximab vedotin. When administered separately or as an admixture, cAC10 and MMAE did not show significant tumor growth inhibition, demonstrating that the ADC is more active than cAC10 or MMAE alone or as an admixture.

Secondary Pharmacodynamics

Cardiac Ventricular Repolarization

No clinically significant prolongation in the duration of ventricular repolarization as measured by QTcF in patients treated with brentuximab vedotin (1.8 mg/kg administered as a 30 min IV infusion) was observed. The QTcF change from baseline was <10 ms (increase) at all evaluated timepoints; brentuximab vedotin was associated with decreases from baseline in the QTc interval (maximum mean decrease from baseline approximately 7 ms). The clinical significance of this finding is unknown. These results are consistent with the hERG assay results in which the IC50 of MMAE on the hERG K^+ channel was estimated to be greater than 100 μM, over 14,000-fold higher than the MMAE C_{max} associated with the 1.8 mg/kg dose of brentuximab vedotin.

TOXICOLOGY

Animal Toxicology

Myelotoxicity

Myelotoxicity was the primary treatment-related toxicity associated with single-dose and repeat-dose IV administration of brentuximab vedotin and MMAE in both monkey and rat. Myelotoxicity was dose-dependent in both species. At the high dose-levels (up to 5 and 9-fold the human systemic exposure (AUC) in monkey and rat, respectively) myelotoxicity was characterized primarily as severe hypocellularity of hematopoietic cells. At exposures up to 3-fold that in human there was minimal hypocellularity and at dose levels similar to or slight less than that in humans no hypocellularity in the bone marrow was observed. At recovery, no bone marrow findings were noted at all dose levels, indicating complete reversibility.

Myelotoxicity-Related Hematologic Toxicity

Consistent with the primary target organ histopathology findings (bone marrow hypocellularity and lymphoid depletion) decreases in peripheral hematology parameters were observed in both monkey and rat. In monkeys, the predominant effect on hematology was a dose-dependent decrease in neutrophils with markedly decreased absolute neutrophil counts at 1 and 2 weeks following each dose with a nadir at 2 weeks postdose, and reversibility by 3 weeks. In addition to the effects on neutrophils, other leukocyte, erythrocyte and reticulocyte counts were variably decreased. In rats, the hematology effects included evidence of significantly reduced erythropoiesis (lower reticulocyte count, red blood cell count, hemoglobin, and hematocrit) resulting in nonregenerative anemia. Within two weeks postdose, complete recovery of all cell lineages was evident in the peripheral hematology endpoints as well as by bone marrow cytology and histopathology.

Neutropenia-Related Mortality

Mortality attributed to bacterial infections secondary to severe neutropenia was observed in 3 of 16 monkeys following administration of one dose of 6 mg/kg brentuximab vedotin. Thus, neutropenia was the most clinically significant toxicity observed in animals.

The primary treatment-related effects of repeat-dose brentuximab vedotin administration to rats and monkeys (bone marrow hypocellularity and lymphoid depletion) and the associated decreases in peripheral blood cells, most notably neutropenia are consistent with pharmacologic disruption of microtubules caused by MMAE.

Neurotoxicity

No histopathologic evidence of neurotoxicity was observed after 4 doses in monkeys or rats at systemic exposures (AUC) up to 6-fold that in humans. In the safety pharmacology study, there were no effects within 4 days following a single-dose of 3 mg/kg brentuximab vedotin to monkeys on neurological endpoints. Additionally, in the 6-month chronic toxicity study in monkeys, after the administration of brentuximab vedotin at 3 mg/kg q3wk x 9, no histopathologic evidence of neurotoxicity was observed.

Hepatotoxicity

Brentuximab vedotin and MMAE treatment resulted in reversible, dose-dependent hepatic toxicity in rats. Focal hepatocellular coagulative necrosis and increases in serum hepatobiliary enzymes, was observed as early as four days post dose in rats administered >5 mg/kg brentuximab vedotin and at the MMAE doses of >0.1 mg/kg.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or MMAE have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Developmental and Reproductive Toxicity

Embryotoxicity

Repeat-dose embryo-fetal development toxicity studies in rats revealed embryo-fetal lethality/teratogenicity. Embryo-fetal lethality and teratogenicity were observed in rats treated with brentuximab vedotin at 1.2 and 4 mg/kg (q3dx5 and 3 and 10 mg/kg (q7dx2), as well as in rats treated with MMAE at 0.2 mg/kg (q7dx2). Embryo-fetal toxicity was characterized by decrease in viable fetuses, increased early resorptions and post-implantation loss. The embryo-fetal toxicity was more severe following administration of 10 mg/kg brentuximab vedotin than MMAE at the molar equivalent dose level (0.2 mg/kg).

Placental transfer of brentuximab vedotin ADC, TAb, and MMAE in pregnant rats was investigated in repeat embryo-fetal development rat studies. Results from both studies were consistent; brentuximab vedotin ADC, TAb, and MMAE were transferred across the placenta of pregnant rats following administration of brentuximab vedotin. Brentuximab vedotin ADC, TAb, and MMAE were detectable in fetal serum, but at lower concentrations than those observed in maternal serum for the same timepoint and dose.

Impairment of Fertility

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male and female reproductive function and fertility.

Repeat-dose studies of brentuximab vedotin and MMAE treatment in rats resulted in partially reversible, dose-dependent testicular toxicity. Seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis and aspermia were observed in rats treated with brentuximab vedotin at 5 and 10 mg/kg (q1wkx4) (approximately 3 times the exposure level of the proposed clinical dose of 1.8 mg/kg) and MMAE at 0.194 and 0.29 mg/kg/dose (q1wx4). In a repeat-dose study of brentuximab vedotin (q1wx4) at 10 mg/kg/dose, partial reversibility of testicular toxicity was demonstrated following a 16-week recovery phase.

Other Toxicities

Brentuximab vedotin and MMAE treatment resulted in reversible, dose-dependent lymphoid depletion (thymus and spleen) and reduction in thymic weight in both rats and monkeys. In addition, brentuximab vedotin administered to rats resulted in sporadic, reversible, observations of cell necrosis in the intestine or pancreas and alveolar histiocytosis in the lung.

Clinical chemistry findings (other than those associated with hepatic toxicities described above) after brentuximab vedotin administration in either rats or monkeys were sporadic, minimal to

mild and included; elevations in total protein, globulin and cholesterol, and slight decreases in albumin.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]ADCETRIS®
(brentuximab vedotin)

Read this carefully before you start taking **ADCETRIS**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ADCETRIS**.

What is ADCETRIS used for?

ADCETRIS is used to treat patients with:

- Hodgkin lymphoma (HL) that has come back after a stem cell transplant or after two types of chemotherapy if you cannot receive a stem cell transplant (see the NOC/c Summary Box below for more detail)
- Systemic anaplastic large cell lymphoma (sALCL) that comes back after treatment with chemotherapy (see the NOC/c Summary Box below for more detail)
- HL at increased risk of continuing or returning, as additional treatment after an autologous stem cell transplant (ASCT)

NOC/c Summary Box

"For the following indications, ADCETRIS has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional."

- Hodgkin lymphoma (HL) that has come back after a stem cell transplant or after two types of chemotherapy if you cannot receive a stem cell transplant
- Systemic anaplastic large cell lymphoma (sALCL) that comes back after treatment with chemotherapy

"For the following indications ADCETRIS has been approved *without conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada."

- HL at increased risk of continuing or returning as additional treatment after an autologous stem cell transplant (ASCT)

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

Serious Warnings and Precautions

In patients treated with ADCETRIS, the following serious side effects have occurred and were fatal in some cases:

- Brain infection causing a serious and potentially fatal condition called progressive multifocal leukoencephalopathy (PML)
- Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis
- Infections
- Pancreatitis (inflammation of the pancreas)
- Gastrointestinal problems
- Lung problems

See below for signs and symptoms of these serious side effects. Immediately report to your doctor if you notice any of the described symptoms.

How does ADCETRIS work?

ADCETRIS (Ad-SET-riss) contains brentuximab vedotin, which is made up of two types of medicine that are attached to each other. One part belongs to a group of medicines called monoclonal antibodies and the other belongs to a group of medicines called anti-mitotics. The monoclonal antibody part allows the drug to find the cancer cell in the body; the anti-mitotic part kills the cancer cell once it is found.

ADCETRIS attaches to a molecule called CD30 that is present on the surface of HL and sALCL cancer cells, but not usually on healthy cells. ADCETRIS then enters the cancer cells and kills them by releasing an anti-mitotic that is toxic to the cancer cells. Even though ADCETRIS usually attaches to cancer cells, and not healthy cells, it can still cause side effects. These should be discussed with your doctor.

What are the ingredients in ADCETRIS?
Medicinal ingredients: brentuximab vedotin
Non-medicinal ingredients: polysorbate 80, sodium citrate, trehalose

ADCETRIS comes in the following dosage forms:
ADCETRIS comes in a single-use vial containing 50 mg of brentuximab vedotin for injection.

Do not use ADCETRIS if:
- You have a known allergy to the medicinal or non-medicinal ingredients.
- You are currently taking another drug called bleomycin. Bleomycin must be stopped before starting ADCETRIS.
- You have or have had progressive multifocal leukoencephalopathy (PML).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADCETRIS. Talk about any health conditions or problems you may have, including if you:
- take a medicine to treat or prevent fungal infections;
- are taking antibiotics for tuberculosis;
- have or have had a liver or kidney disease;
- might be pregnant or are trying to become pregnant;
- are breast feeding;
- are allergic to the ingredients in ADCETRIS.

Other warnings you should know about:
- Women who may become pregnant should use at least 2 reliable methods of birth control during and for 6 months after treatment with ADCETRIS. Immediately report to your doctor if you become pregnant while receiving ADCETRIS.
- Do not breastfeed while you are receiving ADCETRIS. It is not known if the drug can get into breast milk, and therefore, into the baby.
- Men should use an appropriate method of barrier contraception during and for 6 months after treatment with ADCETRIS.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ADCETRIS:
- Some medicines and foods (like grapefruit juice) may change the amount of the anti-mitotic in your body.

How to take ADCETRIS:
ADCETRIS is given as an intravenous infusion over 30 minutes.

Usual dose:
The dose is 1.8 mg/kg. If you have mild liver disease, the dose may be 1.2 mg/kg. If you have more serious liver or serious kidney disease, ADCETRIS use should be avoided. If you weigh more than 100 kg, your dose will be calculated as if your weight was 100 kg. You will receive ADCETRIS at 3-week intervals. Treatment with ADCETRIS will be stopped if your disease gets worse or if you experience unacceptable side effects.

If you are receiving ADCETRIS after an autologous stem cell transplant (ASCT), your treatment should begin within 4–6 weeks after ASCT or recovery from ASCT. Treatment with ADCETRIS will continue for up to 16 doses or until your disease gets worse or if you experience unacceptable side effects.

Overdose:
It is unlikely that you will receive too much ADCETRIS as you will be closely monitored by healthcare professionals during your infusion.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose:
If you miss your appointment to receive ADCETRIS, you should make every effort to receive the missed dose as soon as possible. Doses should not be given less than 3 weeks apart.

What are possible side effects from using ADCETRIS?
These are not all the possible side effects you may feel when taking ADCETRIS. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects associated with the use of ADCETRIS include: nausea, vomiting, fatigue, diarrhea, shortness of breath, low red blood cell counts, and low white blood cell counts. Other side effects you may experience are muscle pain, fever, hair loss and itching. These side effects may occur during and after treatment with ADCETRIS.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON **Nerve damage:** burning sensation, pain, numbness and tingling (feeling of pins and needles) of hands and/or feet, weakness, difficulty walking		X
Infection: fever of ≥38°C or greater, chills, cough, sore throat, or pain on urination		X
Infusion reaction: fever, wheezing or breathing problems, chills, nausea, cough, itching, rash, within 2 days after your dose	X	
Liver damage: yellow coloration to the skin or the		X

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
whites of the eyes		
RARE **Progressive multifocal leukoencephalopathy:** changes in mood or usual behavior, confusion, difficulty with thinking, memory loss, changes in vision or speech, decreased control or sensation in one arm or leg, loss of balance, changes in way of walking. Inform anyone close to you about your treatment since they may notice symptoms of which you are not aware.		X
Tumor lysis syndrome: nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and sudden kidney failure		X
Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis): unexplained widespread skin pain, blisters on your skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of your skin		X
Pancreatitis or other gastrointestinal problems: new or worsening severe abdominal pain, severe nausea, vomiting, or severe diarrhea		X
Lung problems: cough and shortness of breath	X	
High blood sugar: frequent need to urinate, increased thirst, blurred vision	X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store ADCETRIS at 2–8°C in the original carton. Protect from light.

Keep out of reach and sight of children.

If you want more information about ADCETRIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.seagen.com, or by calling 1-855-473-2436.

This leaflet was prepared by Seattle Genetics, Inc.

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