HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS™ (brentuximab vedotin) for Injection

For intravenous infusion

Initial U.S. approval: 2011

----------INDICATIONS AND USAGE----------

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for:

- The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates (1.1).
- The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen (1.2).

These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with ADCETRIS.

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks (2).
- Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

----------DOSAGE FORMS AND STRENGTHS----------

50 mg single-use vial (3).

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- Peripheral neuropathy: Treating physicians should monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Infusion reactions: If an infusion reaction occurs, the infusion should be interrupted and appropriate medical management instituted. If anaphylaxis occurs, the infusion should be discontinued immediately and appropriate medical management instituted (5.2).
- Neutropenia: Monitor complete blood counts prior to each dose of ADCETRIS. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions or discontinuation (5.3).
- Tumor Lysis Syndrome: Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and these patients should be monitored closely and appropriate measures taken (5.4).
- Stevens-Johnson syndrome: If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy (5.5).
- Progressive Multifocal Leukoencephalopathy (PML): A fatal case of PML has been reported in a patient who received 4 chemotherapy regimens prior to receiving ADCETRIS (5.6).
- Use in pregnancy: Fetal harm can occur. Pregnant women should be advised of the potential hazard to the fetus (5.7).

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) are neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics, Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions (7.1).

----------USE IN SPECIFIC POPULATIONS----------

None (8).

See 17 for PATIENT COUNSELING INFORMATION.

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with ADCETRIS.

1.1 Hodgkin Lymphoma

ADCETRIS (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

1.2 Systemic Anaplastic Large Cell Lymphoma

ADCETRIS is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

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

Do not administer as an intravenous push or bolus.

Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

2.2 Dose Modification

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. 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: Neutropenia should be managed by dose delays and reductions. 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.

2.3 Instructions for Preparation and Administration

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [*see References (15)*].

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 for 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 with a weight of >100 kg should be calculated for 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 (36-46˚F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

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

3 DOSAGE FORMS AND STRENGTHS

ADCETRIS (brentuximab vedotin) for Injection single-use vial containing 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. In the HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, 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 *Dose Modification (2.2)*].

5.2 Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. 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.

5.3 Neutropenia

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. Prolonged (≥1 week) severe neutropenia can occur with ADCETRIS. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations [*see Dose Modification (2.2)*].

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome may occur. Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.5 Stevens-Johnson Syndrome

Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.6 Progressive Multifocal Leukoencephalopathy

A fatal case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient who received 4 chemotherapy regimens prior to receiving ADCETRIS.

5.7 Use in Pregnancy

There are no adequate and well-controlled studies of 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 significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting. The most common adverse reactions occurring in at least 10% of patients in either trial, regardless of causality, using the NCI Common Toxicity Criteria Version 3.0, are shown in Table 1.

Experience in Hodgkin Lymphoma

ADCETRIS was studied in 102 patients with HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 27 weeks (range, 3 to 56 weeks) [*see Clinical Studies (14)*].

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting.

Experience in Systemic Anaplastic Large Cell Lymphoma

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 24 weeks (range, 3 to 56 weeks) [*see Clinical Studies (14)*].

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain.

Combined Experience

Table 1: Most Commonly Reported (≥10%) Adverse Reactions

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia*	54	15	6	55	12	9
Anemia*	33	8	2	52	2	-
Thrombocytopenia*	28	7	2	16	5	5
Lymphadenopathy	11	-	-	10	-	-
Nervous system disorders						
Peripheral sensory neuropathy	52	8	-	53	10	-
Peripheral motor neuropathy	16	4	-	7	3	-
Headache	19	-	-	16	2	-
Dizziness	11	-	-	16	-	-

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
General disorders and administration site conditions						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Chills	13	-	-	12	-	-
Pain	7	-	-	28	-	5
Edema peripheral	4	-	-	16	-	-
Infections and infestations						
Upper respiratory tract infection	47	-	-	12	-	-
Gastrointestinal disorders						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Constipation	16	-	-	19	2	-
Skin and subcutaneous tissue disorders						
Rash	27	-	-	31	-	-
Pruritus	17	-	-	19	-	-
Alopecia	13	-	-	14	-	-
Night sweats	12	-	-	9	-	-
Dry skin	4	-	-	10	-	-
Respiratory, thoracic and mediastinal disorders						
Cough	25	-	-	17	-	-
Dyspnea	13	1	-	19	2	-
Oropharyngeal pain	11	-	-	9	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	19	-	-	9	-	-
Myalgia	17	-	-	16	2	-
Back pain	14	-	-	10	2	-
Pain in extremity	10	-	-	10	2	2
Muscle spasms	9	-	-	10	2	-
Psychiatric disorders						
Insomnia	14	-	-	16	-	-
Anxiety	11	2	-	7	-	-

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Metabolism and nutrition disorders						
Decreased appetite	11	-	-	16	2	-
Investigations						
Weight decreased	6	-	-	12	3	-

*Derived from laboratory values and adverse reaction data

Infusion reactions

Two cases of anaphylaxis were reported in phase 1 trials. There were no Grade 3 or 4 infusion-related reactions reported in the phase 2 trials, however, Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). The most common adverse reactions (≥2%) associated with infusion-related reactions were chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).

Serious adverse reactions

In the phase 2 trials, serious adverse reactions, regardless of causality, were reported in 31% of patients receiving ADCETRIS. The most common serious adverse reactions experienced by patients with HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%). The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Other important serious adverse reactions reported included one case each of PML, Stevens-Johnson syndrome and tumor lysis syndrome.

Dose modifications

Adverse reactions that led to dose delays in more than 5% of patients were neutropenia (14%) and peripheral sensory neuropathy (11%) [*see Dose Modification (2.2)*].

Discontinuations

Adverse reactions led to treatment discontinuation in 21% of patients. Adverse reactions that led to treatment discontinuation in 2 or more patients with HL or sALCL were peripheral sensory neuropathy (8%) and peripheral motor neuropathy (3%).

6.2 Immunogenicity

Patients with HL and sALCL in the phase 2 trials [*see Clinical Studies (14)*] were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 7% of patients in these trials developed persistently positive

antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ADCETRIS with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5.

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A [*see Clinical Pharmacology (12.3)*]. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 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%.

7.2 Effect of ADCETRIS on Other Drugs

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 Clinical Pharmacology (12.3)*]. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.7)]*.

There are no adequate and well-controlled studies 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 in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. 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.

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.3 Nursing Mothers

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.

8.4 Pediatric Use

The safety and effectiveness 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.

8.5 Geriatric Use

Clinical trials of ADCETRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Safety and efficacy have not been established.

8.6 Renal Impairment

The kidney is a route of excretion for MMAE. The influence of renal impairment on the pharmacokinetics of MMAE has not been determined.

8.7 Hepatic Impairment

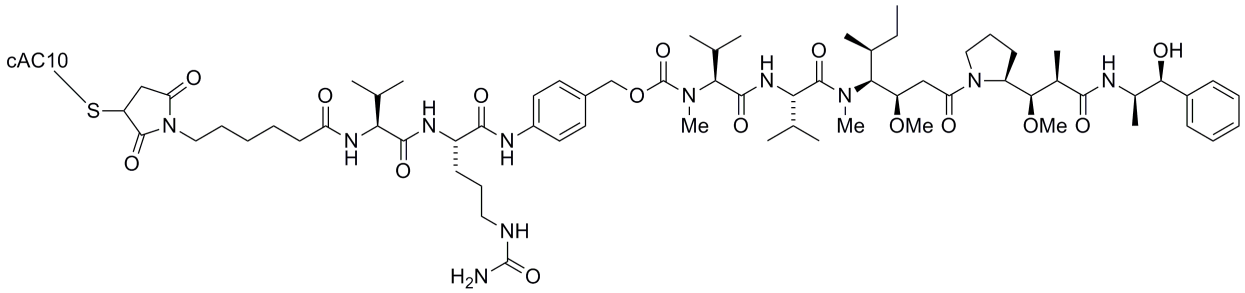
The liver is a route of clearance for MMAE. The influence of hepatic impairment on the pharmacokinetics of MMAE has not been determined.

10 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.

11 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 microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder in single-use vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and 0.20 mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brentuximab vedotin is an ADC. The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a 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.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. Administration of brentuximab vedotin did not prolong the mean QTc interval

>10 ms from baseline. Small increases in the mean QTc interval (<10 ms) cannot be excluded because this study did not include a placebo arm and a positive control arm.

12.3 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 similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

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.

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.

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.

Effects of Gender, Age and Race

Based on the population pharmacokinetic analysis, gender, age and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (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.

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 reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5 or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

14 CLINICAL STUDIES

14.1 Hodgkin Lymphoma

The efficacy of ADCETRIS in patients with HL who relapsed after autologous stem cell transplant was evaluated in one open-label, single-arm, multicenter trial. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 102 patients ranged in age from 15-77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous stem cell transplant.

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

Table 2: Efficacy Results in Patients with Hodgkin Lymphoma

	N=102		
	Percent (95%CI)	Duration of Response, in months	
		Median (95% CI)	Range
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

*Not estimable

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

14.2 Systemic Anaplastic Large Cell Lymphoma

The efficacy of ADCETRIS in patients with relapsed sALCL was evaluated in one phase 2 open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14-76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous stem cell transplant. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

The efficacy results are summarized in Table 3. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 3: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma

	N=58		
	Percent (95%CI)	Duration of Response, in months	
		Median (95% CI)	Range
CR	57 (44, 70)	13.2 (10.8, NE*)	0.7 to 15.9+
PR	29 (18, 41)	2.1 (1.3, 5.7)	0.1 to 15.8+
ORR	86 (77, 95)	12.6 (5.7, NE*)	0.1 to 15.9+

*Not estimable

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

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposure to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials:

- NDC (51144-050-01), 50 mg brentuximab vedotin.

16.2 Storage

Store vial at 2-8˚C (36-46˚F) in the original carton to protect from light.

16.3 Special Handling

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-4].

17 PATIENT COUNSELING INFORMATION

• Peripheral neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness [*see Warnings and Precautions (5.1)*].

• Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5˚F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops [*see Warnings and Precautions (5.3)*].

• Infusion reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion [*see Warnings and Precautions (5.2)*].

• Pregnancy and Nursing

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy. Advise patients to report pregnancy immediately *[see Warnings and Precautions (5.7)]*. Advise patients to avoid nursing while receiving ADCETRIS *[see Use in Specific Populations (8.3)]*.

Manufactured by:
Seattle Genetics, Inc.
Bothell, WA 98021
1-855-473-2436
U.S. License 1853

August 2011