

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 use
Initial U.S. approval: 2011

<p>WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) <i>See full prescribing information for complete boxed warning.</i></p> <p>JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.2).</p>

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	11/2014
Warnings and Precautions (5.6, 5.7, 5.8, 5.10)	11/2014

Indications and Usage

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for 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).
- Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen (1.2).

Accelerated approval was granted for the above indications based on overall response rate. An improvement in patient-reported outcomes or survival has not been established. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Dosage and Administration

- Administer only as an intravenous infusion over 30 minutes every 3 weeks.
- The recommended dose is 1.8 mg/kg (2).
- Reduce dose in patients with mild hepatic impairment (2).
- Continue treatment until disease progression or unacceptable toxicity.

Dosage Forms and Strengths

For injection: 50 mg lyophilized powder in a single-use vial (D).

Contraindications

Concomitant use with bleomycin due to pulmonary toxicity (4).

Warnings and Precautions

- **Peripheral neuropathy:** Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- **Anaphylaxis and infusion reactions:** If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- **Hematologic toxicities:** Monitor complete blood counts prior to each dose of ADCETRIS. Closely monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses (5.3).
- **Serious infections and opportunistic infections:** Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- **Hepatotoxicity:** Monitor liver enzymes and bilirubin (5.8).
- **Serious dermatologic reactions:** Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.10).
- **Embryo-fetal toxicity:** Fetal harm can occur. Advise pregnant women of the potential hazard to the fetus (5.11).

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

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

USE IN SPECIFIC POPULATIONS

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use (5.6, 5.7, 8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

**WARNING: PROGRESSIVE MULTIFOCAL
LEUKOENCEPHALOPATHY (PML)**

1 INDICATIONS AND USAGE

- 1.1 Hodgkin Lymphoma
- 1.2 Systemic Anaplastic Large Cell Lymphoma

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage Recommendations
- 2.2 Dose Modification
- 2.3 Instructions for Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Peripheral Neuropathy
- 5.2 Anaphylaxis and Infusion Reactions
- 5.3 Hematologic Toxicities
- 5.4 Serious Infections and Opportunistic Infections
- 5.5 Tumor Lysis Syndrome
- 5.6 Increased Toxicity in the Presence of Severe Renal Impairment
- 5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
- 5.8 Hepatotoxicity
- 5.9 Progressive Multifocal Leukoencephalopathy
- 5.10 Serious Dermatologic Reactions
- 5.11 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Post Marketing Experience
- 6.3 Immunogenicity

7 DRUG INTERACTIONS

- 7.1 Effect of Other Drugs on ADCETRIS
- 7.2 Effect of ADCETRIS on Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Hodgkin Lymphoma
- 14.2 Systemic Anaplastic Large Cell Lymphoma

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage
- 16.3 Special Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS [see Warnings and Precautions (5.9), Adverse Reactions (6.1)].

1 INDICATIONS AND USAGE

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.

This indication is approved under accelerated approval based on overall response rate [see *Clinical Studies (14.1)*]. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

This indication is approved under accelerated approval based on overall response rate [see *Clinical Studies (14.2)*]. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. See Table 1 for the recommended starting dosage.

Table 1: Recommended ADCETRIS Dosage

	Recommended Starting Dosage
Normal renal and hepatic function	1.8 mg/kg up to 180 mg
Renal impairment	
Mild (creatinine clearance >50–80 mL/min) or moderate (creatinine clearance 30–50 mL/min)	1.8 mg/kg up to 180 mg
Severe (creatinine clearance less than 30 mL/min)	Avoid use [see Warnings and Precautions (5.6)]
Hepatic impairment	
Mild (Child-Pugh A)	1.2 mg/kg up to 120 mg
Moderate (Child-Pugh B) or severe (Child-Pugh C)	Avoid use [see Warnings and Precautions (5.7)]

2.2 Dose Modification

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. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle. In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg.

2.3 Instructions for Preparation and Administration

Administration

- Administer ADCETRIS as an intravenous infusion only.
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Reconstitution

- Follow procedures for proper handling and disposal of anticancer drugs [see *References (15)*].
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
- Determine the number of 50 mg vials needed based on the patient's weight and the prescribed dose [see *Dosage and Administration (2.1)*].
- 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 the 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. If not diluted immediately, 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.

- Withdraw this amount from the vial and immediately add it to an infusion bag containing a minimum volume of 100 mL of 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Gently invert the bag to mix the solution.
- Following dilution, infuse the ADCETRIS solution immediately. If not used immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

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3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation) [see *Adverse Reactions (6.1)*].

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 Anaphylaxis and 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 Hematologic Toxicities

Prolonged (≥ 1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. 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. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses [see *Dose Modification (2.2)*].

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be closely monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

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

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, \geq Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CL_{cr}) <30 mL/min] [see *Use in Specific Populations (8.6)*].

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see *Use in Specific Populations (8.7)*].

5.8 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.

5.9 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.11 Embryo-Fetal Toxicity

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

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Peripheral neuropathy [see *Warnings and Precautions* (5.1)]
- Anaphylaxis and Infusion Reactions [see *Warnings and Precautions* (5.2)]
- Hematologic Toxicities [see *Warnings and Precautions* (5.3)]
- Serious Infections and Opportunistic Infections [see *Warnings and Precautions* (5.4)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.5)]
- Increased Toxicity in the Presence of Severe Renal Impairment [see *Warnings and Precautions* (5.6)]
- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment [see *Warnings and Precautions* (5.7)]
- Hepatotoxicity [see *Warnings and Precautions* (5.8)]
- Progressive Multifocal Leukoencephalopathy [see *Warnings and Precautions* (5.9)]
- Serious Dermatologic Reactions [see *Warnings and Precautions* (5.10)]

- Embryo-Fetal Toxicity [see *Warnings and Precautions (5.11)*]

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 ($\geq 20\%$), 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 2.

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 (14.1)*].

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

Pulmonary Toxicity

In another clinical trial in patients with HL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated [see *Contraindications (4)*].

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 (14.2)*].

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

Combined Experience

Table 2: Most Commonly Reported (≥10%) Adverse Reactions

Adverse Reaction	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Blood and lymphatic system disorders</i>						
Neutropenia*	54	15	6	55	12	9
Anemia*	33	8	2	52	2	-
Thrombocytopenia*	28	7	2	16	5	5
Lymphadenopathy	11	-	-	10	-	-
<i>Nervous system disorders</i>						
Peripheral sensory neuropathy	52	8	-	53	10	-
Peripheral motor neuropathy	16	4	-	7	3	-
Headache	19	-	-	16	2	-
Dizziness	11	-	-	16	-	-
<i>General disorders and administration site conditions</i>						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Chills	13	-	-	12	-	-
Pain	7	-	-	28	-	5
Edema peripheral	4	-	-	16	-	-
<i>Infections and infestations</i>						
Upper respiratory tract infection	47	-	-	12	-	-
<i>Gastrointestinal disorders</i>						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Constipation	16	-	-	19	2	-
<i>Skin and subcutaneous tissue disorders</i>						
Rash	27	-	-	31	-	-
Pruritus	17	-	-	19	-	-
Alopecia	13	-	-	14	-	-
Night sweats	12	-	-	9	-	-
Dry skin	4	-	-	10	-	-

Adverse Reaction	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	25	-	-	17	-	-
Dyspnea	13	1	-	19	2	-
Oropharyngeal pain	11	-	-	9	-	-
<i>Musculoskeletal and connective tissue disorders</i>						
Arthralgia	19	-	-	9	-	-
Myalgia	17	-	-	16	2	-
Back pain	14	-	-	10	2	-
Pain in extremity	10	-	-	10	2	2
Muscle spasms	9	-	-	10	2	-
<i>Psychiatric disorders</i>						
Insomnia	14	-	-	16	-	-
Anxiety	11	2	-	7	-	-
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	11	-	-	16	2	-
<i>Investigations</i>						
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 ($\geq 2\%$) 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 include 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 *Dosage and Administration (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 Post Marketing Experience

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.

Blood and lymphatic system disorders: febrile neutropenia [see *Warnings and Precautions (5.3)*].

Hepatobiliary disorders: hepatotoxicity [see *Warnings and Precautions (5.8)*].

Infections: PML [see *Boxed Warning, Warnings and Precautions (5.9)*], serious infections and opportunistic infections [see *Warnings and Precautions (5.4)*].

Metabolism and nutrition disorders: hyperglycemia.

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

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes [see *Warnings and Precautions (5.10)*].

6.3 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. *In vitro* data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

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%.

P-gp Inhibitors: Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Patients who are receiving P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

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* (5.11)].

Risk Summary

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.

Animal Data

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 ($\geq 99\%$), post-implantation loss ($\geq 99\%$), 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

Avoid the use of ADCETRIS in patients with severe renal impairment (CLcr <30 mL/min) [See *Warnings and Precautions* (5.6)].

The kidney is a route of excretion for monomethyl auristatin E (MMAE). The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CLcr >50-80 mL/min; n=4), moderate (CLcr 30-50 mL/min; n=3) and severe (CLcr <30 mL/min; n=3) renal impairment. In patients with severe renal impairment, the rate of Grade 3 or worse adverse events was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, \geq Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment [See *Warnings and Precautions (5.7)*].

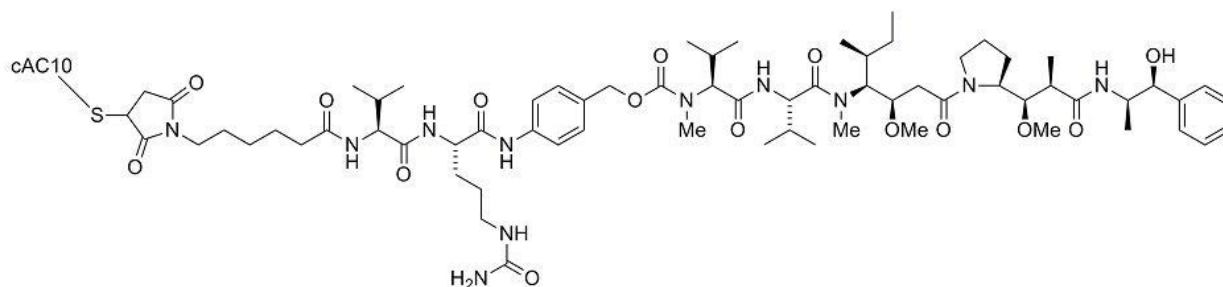
The liver is a route of clearance for MMAE. The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. In patients with moderate and severe hepatic impairment, the rate of \geq Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

10 OVERDOSAGE

There is no known antidote for overdose of ADCETRIS. In case of overdose, 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.

Specific Populations

Renal Impairment: [see Use in Specific Populations (8.6)].

Hepatic Impairment: [see Use in Specific Populations (8.7)].

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 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 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 4. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 4: 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. OSHA Hazardous Drugs. *OSHA*. [Accessed on 30 July 2013, from <http://www.osha.gov/SLTC/hazardousdrugs/index.html>]

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

ADCETRIS is an antineoplastic product. Follow special handling and disposal procedures¹.

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)*].

- Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice [see *Warnings and Precautions (5.8)*].

- Progressive multifocal leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms [see *Boxed Warning, Warnings and Precautions (5.9)*]:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

- Pancreatitis


Advise patients to contact their health care provider if they develop severe abdominal pain [see *Adverse Reactions (6.2)*].

- 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 (5.11)*]. Advise patients to avoid nursing while receiving ADCETRIS [see *Use in Specific Populations (8.1, 8.3)*].



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