ADCETRIS® (brentuximab vedotin) for Injection

For intravenous infusion
Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See Full Prescribing Information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.5, 6.2).

RECENT MAJOR CHANGES
Dosage and Administration (2.1) 08/2013

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 disease progression or unacceptable toxicity.

DOSE FORMS AND STRENGTHS
50 mg single-use vial (3).

CONTRAINDICATIONS
Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity (4).

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 General Dosing Information
2.2 Dose Modification
2.3 Instructions for Preparation and Administration
3 DOSE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Peripheral Neuropathy
5.2 Infusion Reactions
5.3 Neutropenia
5.4 Tumor Lysis Syndrome
5.5 Progressive Multifocal Leukoencephalopathy
5.6 Stevens-Johnson Syndrome
5.7 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 (5.5), Adverse Reactions (6.1)].

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

Do not administer as an intravenous push or bolus.

Continue treatment until disease progression or unacceptable toxicity.

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. G-CSF 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 G-CSF support, 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 [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 weighing greater than 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 (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

Pulmonary toxicity: Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial 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.

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 G-CSF support, 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 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. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.6 Stevens-Johnson Syndrome
Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.
5.7 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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Neutropenia*</td>
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<td>15</td>
<td>6</td>
<td>55</td>
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<td>9</td>
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<tr>
<td>Anemia*</td>
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<td>8</td>
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<td>52</td>
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<tr>
<td>Thrombocytopenia*</td>
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<td>16</td>
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<td>Lymphadenopathy</td>
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<td>Peripheral sensory neuropathy</td>
<td>52</td>
<td>8</td>
<td>-</td>
<td>53</td>
<td>10</td>
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<tr>
<td>Peripheral motor neuropathy</td>
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<td>4</td>
<td>-</td>
<td>7</td>
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<td>Headache</td>
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<td>16</td>
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<tr>
<td>Dizziness</td>
<td>11</td>
<td>-</td>
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<td>16</td>
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<td><strong>General disorders and administration site conditions</strong></td>
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<tr>
<td>Fatigue</td>
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<td>3</td>
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<td>41</td>
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<tr>
<td>Pyrexia</td>
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<td>38</td>
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<td>Chills</td>
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<tr>
<td>Pain</td>
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<td>Edema peripheral</td>
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<td><strong>Infections and infestations</strong></td>
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<td>Upper respiratory tract infection</td>
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<td><strong>Gastrointestinal disorders</strong></td>
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<tr>
<td>Nausea</td>
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<td>38</td>
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<tr>
<td>Diarrhea</td>
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<td>29</td>
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<tr>
<td>Abdominal pain</td>
<td>25</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Vomiting</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>3</td>
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<tr>
<td>Constipation</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>19</td>
<td>2</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<tr>
<td>Rash</td>
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<td>31</td>
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<tr>
<td>Pruritus</td>
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<td>19</td>
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<td>Alopecia</td>
<td>13</td>
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<td>-</td>
<td>14</td>
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<tr>
<td>Night sweats</td>
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<td>-</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dry skin</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>-</td>
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</tr>
</tbody>
</table>

Reference ID: 3359579
### 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

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**Adverse Reaction**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
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<tr>
<td>Cough</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>-</td>
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<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1</td>
<td>-</td>
<td>19</td>
<td>2</td>
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<td>Oropharyngeal pain</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>-</td>
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<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Back pain</td>
<td>14</td>
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<td>-</td>
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<td>Pain in extremity</td>
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<td>-</td>
<td>10</td>
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<tr>
<td>Muscle spasms</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>10</td>
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<td><strong>Psychiatric disorders</strong></td>
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<td>Insomnia</td>
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<td>Anxiety</td>
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<td>7</td>
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<td><strong>Metabolism and nutrition disorders</strong></td>
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<tr>
<td>Decreased appetite</td>
<td>11</td>
<td>-</td>
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<td>16</td>
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<td><strong>Investigations</strong></td>
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<tr>
<td>Weight decreased</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

*Derived from laboratory values and adverse reaction data*
(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 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 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.

Cases of PML have been reported [see Boxed Warning, Warnings and Precautions (5.5)].

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.

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)].

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 (≥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

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

*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

<table>
<thead>
<tr>
<th></th>
<th>N=58</th>
<th>Duration of Response, in months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent (95%CI)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>CR</td>
<td>57 (44, 70)</td>
<td>13.2 (10.8, NE*)</td>
</tr>
<tr>
<td>PR</td>
<td>29 (18, 41)</td>
<td>2.1 (1.3, 5.7)</td>
</tr>
<tr>
<td>ORR</td>
<td>86 (77, 95)</td>
<td>12.6 (5.7, NE*)</td>
</tr>
</tbody>
</table>

*Not estimable
+ Follow up was ongoing at the time of data submission.

15 REFERENCES

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)].

- **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 (5.5)]:

  - 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

- **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)].

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Revised: 8/2013

Reference ID: 3359579