Brentuximab vedotin

Targets (1) Enzymes (1) Transporters (1) Biointeractions (4)

IDENTIFICATION

Name

Brentuximab vedotin

Accession Number

DB08870

Type

Biotech

Groups

Approved, Investigational

Biologic Classification

Protein Based Therapies
Monoclonal antibody (mAb) / Fusion proteins

Description

Brentuximab vedotin, also known as Adcetris®, is an antibody-drug conjugate that combines an anti-CD30 antibody with the drug monomethyl auristatin E (MMAE). It is an anti-neoplastic agent used in the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma. Brentuximab vedotin was initially approved in 2011. In January 2012, the drug label was revised with a boxed warning of a condition known as progressive multifocal leukoencephalopathy and death due to opportunistic JC virus infection post treatment [5].

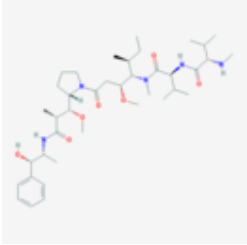
The U.S. Food and Drug Administration approved Adcetris in March 2018 to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL) in combination with chemotherapy [5].

progression, systemic anaplastic large cell lymphoma (ALCL) after the failure of other treatment regimens, and primary cutaneous ALCL after failure of other treatment regimens [5].

Lymphoma is a malignancy that begins in the lymphatic system, which helps to combat infection and disease. Lymphoma may begin anywhere in the body and can spread to nearby lymph nodes. The two main types of lymphoma are Hodgkin lymphoma (also called Hodgkin disease) and non-Hodgkin lymphoma. Most individuals with Hodgkin's lymphoma have the classical type. In this type of lymphoma, large, abnormal lymphocytes (a type of white blood cell) are found in the lymph nodes called Reed-Sternberg cells. With early diagnosis and intervention, patients with Hodgkin lymphoma normally experience long-term remission [5].

The ECHELON-1 study results demonstrated superior efficacy of the drug combined with a chemotherapy regimen when it is compared to the previous standard of care. Importantly, removing the drug bleomycin, a highly toxic agent, was completely removed from the regimen. This demonstrates meaningful progress in treatment for patients affected by this disease [6].

Protein structure



Protein chemical formula

$C_{6476}H_{9930}N_{1690}O_{2030}S_{40}$

Protein average weight

150500.0 Da (range 149200-151800)

Sequences

Not Available

Synonyms

cAC10-vcMMAE

External IDs

SGN-35

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END		
Adcetris	Powder, for solution	50 mg	Intravenous	Seattle Genetics, Inc.	2013-02-19	Not applicable		
Adcetris	Injection, powder, lyophilized, for solution	50 mg/10.5mL	Intravenous	Seattle Genetics, Inc.	2011-08-25	Not applicable		
Adcetris	Injection, powder, for solution	50 mg	Intravenous	Takeda Pharma A/S	2012-10-25	Not applicable		

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Categories

Amino Acids, Peptides, and Proteins

Antibodies

Antibodies, Monoclonal

Antineoplastic Agents

Antineoplastic and Immunomodulating Agents

Blood Proteins

CD30-directed Immunoconjugate

Cytochrome P-450 CYP3A Inhibitors

Cytochrome P-450 CYP3A4 Inhibitors

Cytochrome P-450 CYP3A4 Substrates

Cytochrome P-450 Enzyme Inhibitors

Globulins

Immunoglobulins

Immunoproteins

Immunosuppressive Agents

UNII

7XL5ISS668

CAS number

914088-09-8

PHARMACOLOGY

Indication

Seattle Genetics Announced FDA Approval of ADCETRIS® (Brentuximab Vedotin) in combination with chemotherapy for adults with previously untreated stage III or IV Classical Hodgkin Lymphoma in March 2018 [5, 6].

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 [FDA Label], [5].

Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen [FDA Label].

Structured Indications

B-large cell anaplastic Lymphoma (Kiel Classification) refractory

Refractory Hodgkin Lymphoma

Post-autologous hematopoietic stem cell transplantation Hodgkin lymphoma

Pharmacodynamics

Brentuximab vedotin causes apoptosis of tumor cells by preventing cell cycle progression of the G2 to M phase through disruption of the cytosolic microtuble network, thus preventing tumor growth and proliferation [FDA Label].

Hodgkin lymphoma (HL) is characterized by malignant Reed-Sternberg cells which express CD30, a marker of large cell lymphoma [4]. Until March 2018, USA National Comprehensive Cancer Network guidelines for patients with advanced HL (stage III/IV disease) recommend treatment with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), or escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) as first-line regimens [7].

ABVD appears to be as effective, with fewer side effects, as escalated BEACOPP. Escalated

Brentuximab vedotin, a CD30-directed antibody conjugate, selectively targets malignant HL cells [3].

The effect of Brentuximab vedotin (1.8 mg/kg) on the QTc interval was studied in an open-label, single-group study in 46 patients diagnosed with CD30-expressing hematologic malignancies. Ingestion of brentuximab vedotin did not prolong the mean cardiac QTc interval >10 ms from baseline levels. Smaller increases in the mean QTc interval (<10 ms) cannot be ruled out because this study did not include a placebo arm and a positive control arm [FDA Label].

Mechanism of action

Brentuximab vedotin is composed of 3 parts: a chimeric human-murine IgG1 that selectively targets CD30, monomethyl auristatin E (MMAE), which is a microtubule-disrupting agent, and a protease-susceptible linker that links the antibody and MMAE. The IgG1 antibody enables Brentuximab vedotin to target tumor cells expressing CD30 on their surface. Following this Brentuximab vedotin enters the cell. Once inside, the linker is cleaved releasing MMAE which binds disrupts the microtubule network [FDA Label].

The antibody component of this drug is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule-disrupting particle. MMAE is covalently attached to the antibody by a linker. Data suggest that the anticancer activity of Adcertris is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the subsequent release of MMAE by proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, inducing cell cycle arrest and apoptotis of the malignant cells [FDA Label].

A	Tumor necrosis factor receptor superfamily member 8
	binder
	Human

Absorption

Steady-state of the ADC is achieved within 21 days with every 3-week dosing of Adcetris. Minimal to no accumulation of ADC is observed with multiple doses at the every 3-week schedule. The time to maximum concentration for MMAE ranges from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE is achieved within 21 days with every 3-week dosing of Adcetris. MMAE exposures decrease with continued administration of Adcetris with about 50% to 80% of the

exposure of the first dose being observed at future doses. The AUC of MMAE was measured to be approximately 2.2-fold higher in patients with hepatic impairment in comparison with patients with normal hepatic function [FDA Label]

MMAE is unlikely to displace or to be displaced by highly protein-bound drugs. In vitro studies show that MMAE is a substrate of P-gp and was not a potent inhibitor of P-gp [FDA Label].

Protein binding

In vitro, the binding of MMAE to human plasma proteins is in the range of 68–82% [FDA Label].

Metabolism

Data in both 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 [FDA Label].

Brentuximab vedotin >

Route of elimination

This drug appears follow metabolite kinetics, with the elimination of appearing to be limited by its rate of release from the antibody-drug conjugate (ADC). An excretion study was done in patients receiving a dose of 1.8 mg/kg of Adcetris. About 24% of the total MMAE ingested as part of the ADC during an ADCETRIS infusion was recovered in both urine and feces over a 7-day time frame. Of the recovered MMAE, approximately 72% was found in the feces and the majority of the excreted MMAE was excreted as unchanged drug [FDA Label].

Half life

The terminal half-life is approximately 4-6 days [FDA Label].

Clearance

The liver is the primary route of clearance for MMAE. The pharmacokinetics and safety of Brentuximab vedotin and MMAE were examined after the administration of 1.2 mg/kg of Adcetris to patients with mild, moderate, and severe hepatic impairment. In patients with moderate and severe hepatic impairment, the rate of ≥Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function [FDA Label]. It is recommended to avoid use in patients with severe renal impairment (CrCl <30mL/min) [9].

Toxicity

The most severe toxic reaction seen in patients is progressive multifocal leukoencephalopathy [FDA Label].

worsen progressively. The symptoms vary depending on which region of the brain is infected. In about two out of three patients, mental function deteriorates rapidly, leading to dementia. Speaking and walking may become increasingly difficult. Vision may be impaired, and total blindness may occur. Rarely, headaches and seizures can occur, mainly in immunocompromised patients. The most serious sequela of this condition is death [10].

Common adverse effects of Adcetris may include: neutropenia, anemia, peripheral neuropathy, nausea, fatigue, constipation, diarrhea, vomiting, and fever. In one trial, neutropenia occurred in 91 percent of patients treated with Adcetris plus chemotherapy, which was associated with a 19 percent rate of febrile neutropenia (neutropenia and fever) [5]. Preventive treatment with G-CSF, a growth factor for the bone marrow to produce white blood cells, is recommended with Adcetris plus chemotherapy for the first-line treatment of Stage III or IV cHL [5].

Adcetris has a boxed warning that emphasizes the risk of John Cunningham virus infection leading to progressive multifocal leukoencephalopathy, or PML, a rare but serious brain infection that may be lethal.

Serious risks of Adcetris include peripheral neuropathy, severe allergic (anaphylaxis) or infusion-site reactions; damage to the blood, lungs and liver (hematologic, pulmonary and hepato-toxicities); severe/opportunistic infections; metabolic abnormalities (tumor lysis syndrome); dermatologic reactions and gastrointestinal complications. Adcetris may cause harm to the fetus and newborn baby; women should be warned of the potential risk to the fetus and to use effective contraception, and to avoid breastfeeding while taking Adcetris [5].

MMAE was found to be 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 drug. Fertility studies with Brentuximab vedotin or MMAE have not been conducted. Despite this, results of repeat-dose toxicity studies in rats suggest the potential for Brentuximab vedotin to have a negative effect on male reproductive function and fertility. In a 4-week repeated-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 [5]. Effects in animals were seen mostly at 5 and 10 mg/kg doses of brentuximab vedotin. These dosages are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on individual body weight [FDA Label].

Affected organisms

Humans and other mammals

Pathways

Not Available

INTERACTIONS

Drug Interactions

Search

DRUG	INTERACTION	DRUG GROUP
Abemaciclib	The serum concentration of Brentuximab vedotin can be increased when it is combined with Abemaciclib.	Approved, Investigational
Acetaminophen	The serum concentration of Brentuximab vedotin can be increased when it is combined with Acetaminophen.	Approved
Acetyldigitoxin	Acetyldigitoxin may decrease the cardiotoxic activities of Brentuximab vedotin.	Approved
Acetyldigoxin	Acetyldigoxin may decrease the cardiotoxic activities of Brentuximab vedotin.	Experimental
Afatinib	The serum concentration of Brentuximab vedotin can be increased when it is combined with Afatinib.	Approved
Albendazole	The serum concentration of Brentuximab vedotin can be increased when it is combined with Albendazole.	Approved, Vet Approved
Aldosterone	The serum concentration of Brentuximab vedotin can be decreased when it is combined with Aldosterone.	Experimental, Investigational
Alectinib	The serum concentration of Brentuximab vedotin can be increased when it is combined with Alectinib.	Approved, Investigational
Alfentanil	The serum concentration of Brentuximab vedotin can be increased when it is combined with Alfentanil.	Approved, Illicit
Amantadine	The serum concentration of Brentuximab vedotin can be increased when it is combined with Amantadine.	Approved

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Food Interactions

No interactions found.

REFERENCES

DeBlanc R, Toki BE, Law CL, Doronina SO, Siegall CB, Senter PD, Wahl AF: cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003 Aug 15;102(4):1458-65. Epub 2003 Apr 24

General References

1. Francisco JA, Cerveny CG, Meyer DL, Mixan BJ, Klussman K, Chace DF, Rejniak SX, Gordon KA, DeBlanc R, Toki BE, Law CL, Doronina SO, Siegall CB, Senter PD, Wahl AF: cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003 Aug 15;102(4):1458-65. Epub 2003 Apr 24. [PubMed:12714494]
2. Eichenauer DA, Plutschow A, Kreissl S, Sokler M, Hellmuth JC, Meissner J, Mathas S, Topp MS, Behringer K, Klapper W, Kuhnert G, Dietlein M, Kobe C, Fuchs M, Diehl V, Engert A, Borchmann P: Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. Lancet Oncol. 2017 Dec;18(12):1680-1687. doi: 10.1016/S1470-2045(17)30696-4. Epub 2017 Nov 10. [PubMed:29133014]
3. Cao H, Yamamoto K, Yang LX, Weber R: Brentuximab vedotin: first-line agent for advanced Hodgkin lymphoma. Anticancer Res. 2013 Sep;33(9):3879-85. [PubMed:24023323]
4. Horie R, Watanabe T: CD30: expression and function in health and disease. Semin Immunol. 1998 Dec;10(6):457-70. doi: 10.1006/smim.1998.0156. [PubMed:9826579]
5. FDA expands approval of Adcetris for first-line treatment of Stage III or IV classical Hodgkin lymphoma in combination with chemotherapy [Link]
6. Seattle Genetics Announces FDA Approval of ADCETRIS® (Brentuximab Vedotin) in Combination with Chemotherapy for Adults with Previously Untreated Stage III or IV Classical Hodgkin Lymphoma Read more: http://www.digitaljournal.com/pr/3703005#ixzz5AKAaxmbe [Link]
7. NCCN Flash UpdatesTM: NCCN Guidelines® and NCCN Compendium® Updated [Link]
8. EMA label [Link]
9. Cancer Care Ontario Formulary [Link]
10. Merck Manuals, Progressive Multifocal Leukoencephalopathy [Link]
11. Seattle genetics Brentuximab Vedotin [Link]
12. Brentuximab vedotin: clinical updates and practical guidance [Link]

External Links

KEGG Drug

D09587

PubChem Substance

347910376

ChEMBL

CHEMBL1742994

RxList

RxList Drug Page

Wikipedia

Brentuximab_vedotin

ATC Codes

L01XC12 — Brentuximab vedotin

- L01XC — Monoclonal antibodies
- L01X — OTHER ANTINEOPLASTIC AGENTS
- L01 — ANTINEOPLASTIC AGENTS
- L — ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

AHFS Codes

10:00.00 — Antineoplastic Agents

FDA label

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CLINICAL TRIALS

Clinical Trials

Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
0	Active Not Recruiting	Treatment	Malignant Lymphomas	1
1	Active Not Recruiting	Treatment	Acute Myelogenous Leukaemia (AML)	1
1	Active Not Recruiting	Treatment	Leukemia Acute Myeloid Leukemia (AML) / Leukemia, Lymphoblastic, Acute / Myelodysplastic Syndromes	1
1	Active Not Recruiting	Treatment	Lymphoma, Hodgkins / Refractory / Relapses	1
1	Active Not Recruiting	Treatment	Lymphoma, Large B-Cell, Diffuse (DLBCL)	1
1	Completed	Treatment	Anaplastic Large-Cell Lymphoma / Lymphoma, Hodgkins	1
1	Completed	Treatment	Carcinoma NOS / Hodgkins Disease (HD) / Lymphoma, Large-Cell, Anaplastic / Neoplasms / Non-Hodgkin's Lymphoma (NHL)	1

1	Completed	Treatment	Hodgkins Disease (HD)	1
1	Completed	Treatment	Hodgkins Disease (HD) / Lymphoma, Large-Cell, Anaplastic / Non-Hodgkin's Lymphoma (NHL)	2

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PHARMACOECONOMICS

Manufacturers

Not Available

Packagers

Not Available

Dosage forms

Search

FORM	ROUTE	STRENGTH
Injection, powder, for solution	Intravenous	50 mg
Injection, powder, lyophilized, for solution	Intravenous	50 mg/10.5mL
Powder, for solution	Intravenous	50 mg

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Prices

Not Available

Patents

Not Available

PROPERTIES

State

Experimental Properties

Not Available

TAXONOMY

Description

Not Available

Kingdom

Organic Compounds

Super Class

Organic Acids

Class

Carboxylic Acids and Derivatives

Sub Class

Amino Acids, Peptides, and Analogues

Direct Parent

Peptides

Alternative Parents

Not Available

Substituents

Not Available

Molecular Framework

Not Available

External Descriptors

Not Available

1. Tumor necrosis factor receptor superfamily member 8

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Binder

General Function

Tumor necrosis factor-activated receptor activity

Specific Function

Receptor for TNFSF8/CD30L. May play a role in the regulation of cellular growth and transformation of activated lymphoblasts. Regulates gene expression through activation of NF-kappa-B.

Gene Name

TNFRSF8

Uniprot ID

P28908

Uniprot Name

Tumor necrosis factor receptor superfamily member 8

Molecular Weight

63746.47 Da

References

1. Francisco JA, Cerveny CG, Meyer DL, Mixan BJ, Klussman K, Chace DF, Rejniak SX, Gordon KA, DeBlanc R, Toki BE, Law CL, Doronina SO, Siegall CB, Senter PD, Wahl AF: cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003 Aug 15;102(4):1458-65. Epub 2003 Apr 24. [PubMed:12714494]
2. Seattle genetics Brentuximab Vedotin [Link]

ENZYMES

1. Cytochrome P450 3A4

Kind

Protein

Organism

Human

Pharmacological action

No

Actions

Substrate | Inhibitor

General Function

Vitamin d3 25-hydroxylase activity

Specific Function

Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It performs a variety of oxidation react...

Gene Name

CYP3A4

Uniprot ID

P08684

Uniprot Name

Cytochrome P450 3A4

Molecular Weight

57342.67 Da

References

1. Cancer Care Ontario Formulary [Link]

TRANSPORTERS

1. ATP-binding cassette sub-family B member 5

Kind

Protein

Organism

Human

Pharmacological action

Unknown

Actions

Substrate

General Function

Efflux transmembrane transporter activity

Specific Function

Drug efflux transporter present in a number of stem cells that acts as a regulator of cellular differentiation. Able to mediate efflux from cells of the rhodamine dye and of the therapeutic drug do...

Gene Name

ABCB5

Uniprot ID

Q2M3G0

Uniprot Name

ATP-binding cassette sub-family B member 5

Molecular Weight

138639.48 Da

References

1. Brentuximab vedotin: clinical updates and practical guidance [Link]

Drug created on May 01, 2013 14:50 / Updated on May 15, 2018 11:52

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