ADCETRIS - APPROVED PACKAGE INSERT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINAL PRODUCT

ADCETRIS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of brentuximab vedotin.

After reconstitution (see **Section 6.6**), each mL contains 5 mg of brentuximab vedotin.

Excipient with known effect

Each vial contains approximately 13,2 mg of sodium.

For the full list of excipients, see **Section 6.1**.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

All indications are applicable to patients with cancers that are CD30 positive.

ADCETRIS is indicated for the frontline treatment of adult patients with advanced Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine.

ADCETRIS is indicated for the treatment of adult patients with HL at risk of relapse or progression following autologous stem cell transplant (ASCT).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory Hodgkin lymphoma (HL).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

ADCETRIS is indicated for the treatment of adult patients with cutaneous T-cell lymphoma (CTCL) who require systemic therapy.

4.2 Posology and method of administration

Posology

ADCETRIS should be administered under the supervision of a medical practitioner experienced in the use of anticancer agents.

- ***Frontline HL:***

The recommended dose **in combination** with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]) is 1,2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles (see **Section 5.1**).

Primary prophylaxis with growth factor support (granulocyte colony stimulating factor (G-CSF)) is recommended for all patients beginning with the first dose (see **Section 4.4,** Febrile neutropenia).

Refer to the package insert of chemotherapy agents given in combination with **ADCETRIS** for frontline treatment of patients with HL.

- ***HL at risk of relapse or progression:***

The recommended dose is 1,8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

For patients with HL at risk of relapse or progression following ASCT, **ADCETRIS** treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles.

- ***Relapsed or refractory HL***

- ***Relapsed or refractory sALCL:***

The recommended dose is 1,8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended starting dose for the **retreatment** of patients who have previously responded to treatment with **ADCETRIS** is 1,8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose. Treatment should be continued until disease progression or unacceptable toxicity (see **Section 4.4**). Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see **Section 5.1**).

- ***Cutaneous T-cell lymphoma (CTCL)***

The recommended dose is 1,8 mg/kg administered as an intravenous infusion over 30 minutesr every 3 weeks. Patients with CTCL should receive up to 16 cycles.

If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see **Determining dosage amount**). Complete blood counts should be monitored prior to administration of each dose of this treatment (see **Section 4.4**). Patients should be monitored during and after infusion (see **Section 4.4**).

Special patient populations:

Renal and Hepatic impairment

Combination therapy

Patients with renal impairment should be closely monitored for adverse events. There is no clinical trial experience using **ADCETRIS** in combination with chemotherapy in patients with severe renal impairment.

Patients with hepatic impairment should be closely monitored for adverse events. There is no clinical trial experience using **ADCETRIS** in combination with chemotherapy in patients with hepatic impairment, where total bilirubin is > 1,5 times the upper limit of normal (ULN) (unless due to Gilbert syndrome), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are >3 times the ULN, or >5 times the ULN if their elevation may be reasonably ascribed to the presence of HL in the liver **(see Section 5.2)**.

Monotherapy

The recommended starting dose in patients with severe renal impairment is 1,2 mg/kg administered as an

intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events (see **Section 5.2**).

The recommended starting dose in patients with hepatic impairment is 1,2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events.

Elderly

The dosing recommendations for patients aged 65 and older are the same as for adults (see **Section 5.2**).

Paediatric population

The safety and efficacy of children less than 18 years have not yet been established. See **Section 5.2** for new data. In nonclinical studies, thymus depletion has been observed.

Dose adjustments

Neutropenia

If neutropenia develops during treatment it should be managed by dose delays. See **Table 1** below for appropriate dosing recommendations (see also **Section 4.4**).

Table 1: Dosing recommendations for neutropenia

Severity grade of neutropenia (signs and symptoms – abbreviated description of CTCAE [a])	**Modification of dosing schedule (monotherapy)**	**Modification of dosing schedule (combination therapy)**
Grade 1 (<LLN – 1 500/mm^3 <LLN – 1,5 x 10^9/L) or Grade 2 (<1 500 – 1 000/mm^3 <1,5 – 1,0 x 10^9/L)	Continue with the same dose and schedule	Continue with the same dose and schedule
Grade 3 (<1 000 – 500/mm^3 <1,0 – 0,5 x 10^9/L) or Grade 4 (<500/mm^3 <0,5 x 10^9/L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline, then resume treatment at the same dose and schedule [b]. Consider growth factor support (G-CSF or GM-CSF) in	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule.

	subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.	

[a] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes; LLN =lower limit of normal

[b] Patients who develop Grade 3 or Grade lymphopenia may continue treatment without interruption.

Peripheral neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment see **Table 2** below for appropriate dosing recommendations (see also **Section 4.4**).

Table 2: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy

Severity of peripheral sensory or motor neuropathy (signs and symptoms – abbreviated description of CTCAE [a])	**Modification of dosing schedule (monotherapy)**	**Modification of dosing schedule (combination therapy)**
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with the same dose and schedule	Continue with the same dose and schedule
Grade 2 (interfering with function but not with activities of daily living) or Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then resume treatment at a reduced dose of 1,2 mg/kg every 3 weeks.	Reduce dose to 0,9 mg/kg every 2 weeks
Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1,2 mg/kg every 3 weeks	Withhold treatment with brentuximab vedotin until toxicity is ≤ Grade 2, then restart treatment at a reduced dose to 0,9 mg/kg every 2 weeks. Consider modifying the dose of other neurotoxic agents as per their package inserts.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment	Discontinue treatment

[a] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Method of administration

The recommended dose of **ADCETRIS** is infused over 30 minutes. For instructions on reconstitution and dilution of **ADCETRIS** before administration, see below. **ADCETRIS** must not be administered as an intravenous push or bolus. **ADCETRIS** should be administered through a dedicated intravenous line and it must not be mixed with other medicines.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Combined use of bleomycin and **ADCETRIS** causes pulmonary toxicity.

ADCETRIS is contraindicated in women who are pregnant or are breastfeeding their infants (see **Section 4.6**). Men being treated with **ADCETRIS** are advised not to father a child during treatment and for up to 6 months following the last dose (see **Section 4.6**).

4.4 Special warnings and precautions for use

Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in ADCETRIS-treated patients.

PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. **ADCETRIS** dosing should be stopped in any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. **ADCETRIS** dosing should be permanently discontinued if a diagnosis of PML is confirmed. The medical practitioner should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pancreatitis

Acute pancreatitis has been observed in patients treated with ADCETRIS. Fatal outcomes have been reported. Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. ADCETRIS should be held for any suspected case of acute pancreatitis. ADCETRIS should be discontinued if a diagnosis of acute pancreatitis is confirmed

Pulmonary Toxicity

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving **ADCETRIS**. Although a causal association with ADCETRIS has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider withholding **ADCETRIS** dosing during evaluation and until symptomatic improvement.

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis / septic shock (including fatal outcomes) and herpes zoster, and opportunistic infections such as Pneumocystis jiroveci (carinii) pneumonia and oral candidiasis have been reported in patients treated with **ADCETRIS**. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-related reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm. Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of **ADCETRIS** should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior infusion-related reaction should be pre-medicated for subsequent infusions. Pre-medication may include paracetamol, an antihistamine and a corticosteroid. Infusion-related reactions are more frequent and more severe in patients with antibodies to **ADCETRIS**.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with **ADCETRIS**. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Peripheral neuropathy

ADCETRIS treatment may cause a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. **ADCETRIS**-induced peripheral neuropathy is typically an effect of cumulative exposure to **ADCETRIS**. In the phase 2 population, at the time of last evaluation, the majority of patients (62 %) had improvement or resolution of their peripheral neuropathy symptoms. Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require discontinuation of **ADCETRIS** (see **Section 4.2**).

Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia and prolonged (≥ 1 week) Grade 3 or Grade 4 neutropenia can occur with **ADCETRIS** which may increase the risk of patients developing serious infections. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, refer to **Section 4.2.**

Febrile neutropenia

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count, 1,0 x 10^9 / L, fever ≥ 38,5 °C) has been reported with treatment with **ADCETRIS**. **ADCETRIS** may cause fatal Grade 5 febrile neutropenia after a single dose of 3,5 mg/kg. Complete blood counts should be monitored prior to administration of each dose of **ADCETRIS**. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops (see **Section 4.2**). When **ADCETRIS** is administered in combination with chemotherapy, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose.

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with **ADCETRIS**. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, treatment with **ADCETRIS** should be discontinued and appropriate medical therapy should be administered.

Gastrointestinal Complications

Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with **ADCETRIS**. Some cases of GI perforations were reported in patients with GI involvement of underlying lymphoma. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Hepatotoxicity

Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with **ADCETRIS**. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk.

Liver function should be routinely monitored in patients receiving **ADCETRIS.**

Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of **ADCETRIS** (see **Section 4.8**).

Hyperglycaemia

Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

Renal and hepatic impairment

There is limited experience in patients with renal and hepatic impairment. Population pharmacokinetic (PK) analysis indicated that MMAE clearance might be affected by moderate and severe renal impairment, and by low serum albumin concentrations (see **Section5.2**).

Co-treatment with ritonavir

No information is available on the co-treatment with ritonavir-containing ART regimens in HIV-infected patients (see Section 4.5 for available information on co-administration of ADCETRIS with CYP3A4 inhibitors).

Immunogenicity

In clinical trials, patients were periodically tested for antibodies to brentuximab vedotin using a sensitive electrochemiluminescent immunoassay. There was a higher incidence of infusion-related reactions observed in patients with antibodies to brentuximab vedotin relative to patients who tested transiently positive or negative. The presence of antibodies to **ADCETRIS** did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of **ADCETRIS**. While the presence of antibodies to **ADCETRIS** does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive ATA (30 %) relative to patients with transiently positive ATA (12 %) and never positive ATA (7 %).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with medicines metabolised through CYP3A4 route (CYP3A4 inhibitors/inducers)

Co-administration of **ADCETRIS** with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73 %, and did not alter the plasma exposure to **ADCETRIS**. Therefore, co-administration of **ADCETRIS** with strong CYP3A4 and P-gp inhibitors may increase the **incidence of neutropenia. If neutropenia develops, refer to Table 3: Dosing recommendations for neutropenia (see Section 4.2**).

Co-administration of **ADCETRIS** with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to **ADCETRIS**; however it reduced exposure to MMAE by approximately 31 %.

Co-administration of midazolam, a CYP3A4 substrate, with **ADCETRIS** did not alter the metabolism of midazolam; therefore **ADCETRIS** is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

Doxorubicin, Vinblastine and Dacarbazine

The serum and plasma pharmacokinetic characteristics of brentuximab vedotin and MMAE respectively following administration of **ADCETRIS** in combination with doxorubicin, vinblastine and dacarbazine were similar to that in monotherapy. Co-administration of **ADCETRIS** did not affect the plasma exposure of doxorubicin, vinblastine or dacarbazine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be using two methods of effective contraception during treatment with **ADCETRIS** and until 6 months after treatment.

Pregnancy

ADCETRIS is contraindicated in women who are pregnant or intend to become pregnant (see **Section 4.3**). Studies in animals have shown reproductive toxicity. See the fertility section below pertaining to advice for women whose male partners are being treated with **ADCETRIS**.

Breastfeeding

Women who are using **ADCETRIS** should not breastfeed their infants.

Male Fertility

In non-clinical studies, **ADCETRIS** treatment has resulted in testicular toxicity, and may alter male fertility.

Men being treated with ADCETRIS are advised to have sperm samples frozen and stored before treatment. Men being treated with ADCETRIS are advised not to father a child during treatment and for up to 6 months following the last dose.

4.7 *Effects on ability to drive and use machines:*

ADCETRIS may have an influence on the ability to drive and use machines and the individual patient's response must be assessed.

Sodium content in excipients

This medicine contains 13,2 mg sodium per vial, equivalent to 0,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of **ADCETRIS** is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below and in **Table 3** have been determined based on data generated from clinical studies.

Monotherapy

In the pooled dataset of **ADCETRIS** as monotherapy across HL, sALCL and CTCL studies the most frequent adverse reactions (≥10 %) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain. Serious adverse drug reactions occurred in 12 % of patients. The frequency of unique serious adverse drug reactions was ≤1 %.

Adverse events led to treatment discontinuation in 24 % of patients receiving **ADCETRIS**.

The safety data in patients retreated with **ADCETRIS** were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28 % vs. 9 % in the pivotal phase 2 studies) and was primarily Grade 2.

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The safety data in patients retreated with **ADCETRIS** were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28 % vs. 9 % in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data in patients with relapsed or refractory HL who had not received an autologous stem cell transplant and were treated with the recommended dose of 1,8 mg/kg every three weeks in a single-arm phase 4 study (n=60), the phase 1 dose escalation and clinical pharmacology studies (n=15 patients) and in the NPP (n=26 patients) were consistent with the safety profile of the pivotal clinical studies.

Combination therapy

For safety information of chemotherapy agents given in combination with **ADCETRIS** (doxorubicin, vinblastine and dacarbazine) for frontline treatment of patients with HL, refer to their package inserts.

In the study of **ADCETRIS** as combination therapy in 662 patients with advanced frontline HL, the most common adverse reactions (≥10 %) were: neutropenia, nausea, constipation, vomiting, fatigue, peripheral sensory neuropathy, diarrhoea, pyrexia, alopecia, peripheral neuropathy, decreased weight, abdominal pain, anaemia, stomatitis, febrile neutropenia, bone pain, insomnia, decreased appetite, cough, headache, arthralgia, neutrophil count decreased, dyspepsia, paraesthesia, back pain, dyspnoea, pain in extremity, myalgia, oropharyngeal pain, upper respiratory tract infection, alanine aminotransferase increased.

In patients receiving **ADCETRIS** combination therapy, serious adverse reactions occurred in 36 % of patients. Serious adverse reactions occurring in ≥3 % of patients included febrile neutropenia (17 %), pyrexia (6 %), and neutropenia (3 %).

Additionally, there were more serious adverse events reported in the elderly patient population (≥65 years of age) in both arms.

Adverse events led to treatment discontinuation in 13 % of patients. Adverse events that led to treatment discontinuation in ≥2 % of patients included peripheral sensory neuropathy, peripheral neuropathy, and peripheral motor neuropathy.

Side effects have been classified according to system organ class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from available data).

Table 3: The Adverse reactions for ADCETRIS

System organ class	**Adverse reactions (monotherapy)**	**Adverse reactions (combination therapy)**
Infections and infestations		

Very common:	Infection[a], upper respiratory tract infection	Infection[a], upper respiratory tract infection
Common:	Sepsis/septic shock, herpes zoster, pneumonia, herpes simplex	Pneumonia, oral candiasis, sepsis / septic shock, herpes simplex
Uncommon:	Oral candidiasis, Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation	Herpes zoster, Pneumocystis jiroveci pneumonia
Frequency not known:	Progressive multifocal leukoencephalopathy	
Blood and lymphatic system disorders		
Very common:	Neutropenia	Neutropenia[a], anaemia, febrile neutropenia
Common:	Anaemia, thrombocytopenia	Thrombocytopenia
Frequency not known:	Febrile neutropenia	
Immune system disorders		
Uncommon:		Anaphylactic reaction
Frequency not known:	Anaphylactic reaction	
Metabolism and nutrition disorders		
Very common:		Decreased appetite
Common:	Hyperglycaemia	Hyperglycaemia
Uncommon:	Tumour lysis syndrome	Tumour lysis syndrome
Nervous system disorders		
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy	Peripheral sensory neuropathy, peripheral motor neuropathy[a], dizziness
Common:	Dizziness, demyelinating	

	polyneuropathy	
Respiratory, thoracic and mediastinal disorders		
Very common:	Cough, dyspnea	Cough, dyspnoea
Gastro-intestinal disorders		
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain	Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis
Uncommon:	Pancreatitis acute	Pancreatitis acute
Hepatobiliary disorders		
Very common:		Alanine aminotransferase (ALT) increased
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Aspartate aminotransferase (AST) increased
Skin and subcutaneous tissue disorders		
Very common:	Alopecia, pruritus	Alopecia, rash[a]
Common:	Rash[a]	Pruritus
Uncommon:		Stevens-Johnson syndrome[b]
Rare:	Stevens-Johnson syndrome/toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders		
Very common:	Myalgia, arthralgia	Bone pain, arthralgia, back pain, myalgia
Common:	Back pain	
General disorders and administration site conditions		
Very common:	Fatigue, chills, pyrexia, infusion-related reactions[a]	Fatigue, pyrexia

Common:		Infusion-related reactions[a], chills
Investigations		
Very common:	Weight decreased	Weight decreased
Psychiatric Disorders		
Very common:		Insomnia

a. Represents pooling of preferred terms.

b. Toxic epidermal necrolysis was not reported in the combination therapy setting.

Adverse reactions that led to dose delays of up to 3 weeks in more than 5 % of patients were neutropenia (14 %) and peripheral sensory neuropathy (11 %) (see **Section 4.2**). The adverse reaction that led to a dose reduction in more than 5 % of patients was peripheral sensory neuropathy (8 %). Ninety percent (90 %) of patients in the phase 2 studies remained at the recommended dose of 1,8 mg/kg while on treatment.

Post-marketing experience

In addition to the adverse reactions included above, the following events have been reported in the post-marketing setting.

Gastrointestinal disorders:

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

Hepatobiliary disorders: hepatotoxicity (including fatal outcomes).

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis (including fatal outcomes).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important.

It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via "**6.04 Adverse Drug Reactions Reporting Form**"

found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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 (see **Section 4.4**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

A 26 Cytostatic agents.

Mechanism of Action

Brentuximab vedotin is a genetically engineered Antibody Drug Conjugate (ADC) that delivers a selective antibody to CD30-expressing tumour cells, thereby causing apoptotic death of these cells. Non-clinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, monomethyl auristatin E (MMAE), is released via proteolytic cleavage.

Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

Classical Hodgkin Lymphoma (HL), systemic Anaplastic Large Cell Lymphoma (sALCL) and subtypes of cutaneous T-cell lymphoma, CTCL, (including MF and pcALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention.

Because of the CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL, sALCL and CD 30+ CTCL disease and therapeutic spectrums and clinical evidence in CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL, sALCL with or without prior ASCT and CD30+CTCL after at least 1 prior systemic therapy. Contributions to the mechanism of action by other antibody associated functions have not been excluded.

5.2 Pharmacokinetic properties

Monotherapy

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion.

Maximum concentrations of brentuximab vedotin antibody-drug conjugate (ADC) were typically observed at the end of infusion or the sampling time point closest to the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule, consistent with the terminal half-life estimate. Typical C_{max} and AUC of ADC after a single 1,8 mg/kg in a phase 1 study was approximately 31,98 µg/ml and 79,41 µg/ml x day, respectively.

Monomethyl auristatin E (MMAE) is the major metabolite of brentuximab vedotin. Median C_{max}, AUC and T_{max} of MMAE after a single 1,8 mg/kg of the ADC in a phase 1 study was approximately 4,97 ng/ml, 37,03 ng/ml x day and 2,09 days, respectively. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50 % to 80 % of the exposure of the first dose being observed at subsequent doses. In the first cycle, higher MMAE exposure was associated with an absolute decrease in neutrophil count.

Combination therapy

The pharmacokinetics of ADCETRIS in combination with doxorubicin, vinblastine, and dacarbazine (AVD) were evaluated in a single phase 3 study in 661 patients. Population pharmacokinetic analysis indicated that the pharmacokinetics of ADCETRIS in combination with AVD were consistent to that in monotherapy.

After multiple-dose, IV infusion of 1,2 mg/kg brentuximab vedotin every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multi-exponential decline with a $t_{1/2z}$ of approximately 4 to 5 days. Maximal plasma concentrations of MMAE were observed approximately 2 days after the end of infusion, and exhibited a mono-exponential decline with a $t_{1/2z}$ of approximately 3 to 4 days.

After multiple-dose, IV infusion of 1,2 mg/kg brentuximab vedotin every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the PK of ADC did not appear to change with time. ADC accumulation (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) was 1,27-fold. The exposure of MMAE (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) appeared to decrease with time by approximately 50 %.

Distribution

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82 %. *In vitro*, MMAE was a substrate of P-gp and was not an inhibitor of P-gp at clinical concentrations. In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC. Based on population PK estimation the typical apparent volume of distribution (VM and VMP) of MMAE were 7,37 L and 36,4 L, respectively.

Metabolism

The ADC is catabolised as a protein with component amino acids recycled or eliminated. *In vivo* data in humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolised. The levels of MMAE metabolites have not been measured in human plasma. At least one metabolite of MMAE has been shown to be active *in vitro.* MMAE is a substrate of CYP3A4 and possibly CYP2D6. *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 only CYP3A4/5 at concentrations much higher than was achieved

during clinical application. MMAE does not inhibit other isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination

The ADC is eliminated by catabolism with a typical estimated CL and half-life of 1,457 l/day and 4-6 days respectively. The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half-life of MMAE was 19,99 l/day and 3-4 days respectively. An excretion study was undertaken in patients who received a dose of 1,8 mg/kg of brentuximab vedotin. Approximately 24 % of the total MMAE administered as part of the ADC during a brentuximab vedotin infusion was recovered in both urine and faeces over a 1-week period. Of the recovered MMAE, approximately 72 % was recovered in the faeces. A lesser amount of MMAE (28 %) was excreted in the urine.

Pharmacokinetics in special populations

Population PK analysis showed that baseline serum albumin concentration was a significant covariate of MMAE clearance. The analysis indicated that MMAE clearance was 2-fold lower in patients with low serum albumin concentrations <3,0 g/dl compared with patients with serum albumin concentrations within the normal range.

Renal impairment

The kidney is a route of excretion of the unchanged active metabolite MMAE. ~~Population~~ A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1,2 mg/kg of ADCETRIS to patients with mild (n=4), moderate (n=3) and severe (n=3) renal impairment. Compared to patients with normal renal function, MMAE exposure increased approximately 1,9-fold (90 % CI 0,85-4,21-fold) in patients with severe renal impairment (creatinine clearance < 30 ml/min). No effect was observed in patients with mild or moderate renal impairment. (see **Section 4.4**).

Hepatic impairment

The liver is a major route of elimination of the unchanged active metabolite MMAE. A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1,2 mg/kg of **ADCETRIS** to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 2,3-fold (90 % CI 1,27-4,12-fold) in patients with hepatic impairment. (see **Section 4.4**).

Elderly patients

The population pharmacokinetics of brentuximab vedotin as monotherapy were examined from several monotherapy studies, including data from 380 patients up to 87 years old (34 patients ≥65-<75 and 17 patients ≥75 years of age). Additionally, the population pharmacokinetics of brentuximab vedotin in combination with AVD were examined, including data from 661 patients up to 82 years old (42 patients ≥65-<75 and 17 patients ≥75 years of age). The influence of age on pharmacokinetics was investigated in each analysis and it was not a significant covariate.

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 1,4 mg/kg or 1,8 mg/kg given every 3 weeks were evaluated in a phase 1/2 clinical trial of 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n=12 and adolescents aged 12 to 17 years, n=24).The C_{max} of ADC was typically observed at the end of infusion or the sampling closest to the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 5 days.

Exposures were approximately dose proportional with a trend observed for lower ADC exposures at lower ages/ body weights in the study population. Median ADC AUC in children and adolescents from this study was approx. 14 % and 3 % lower than in adult patients, respectively, while MMAE exposures were 53 % lower and 13 % higher, respectively, than in adult patients.

Median C_{max} and AUC of ADC after a single 1,8 mg/kg dose were 29,8 µg/mL and 67,9 µg*day/mL, respectively, in patients <12 years of age and 34,4 µg/mL and 77,8 µg*day/mL, respectively, in patients ≥12 years of age. Median C_{max}, AUC, and T_{max} of MMAE after a single 1,8 mg/kg dose were 3,73 ng/mL, 17,3 ng*day/mL, and 1,92 days, respectively, in patients <12 years of age and 6,33 ng/mL, 42,3 ng*day/mL, and 1,82 days, respectively, in patients ≥12 years of age. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged <12 years (0 of 11) and 2 patients aged ≥12 years (2 of 23) became persistently ADA positive.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (for pH-adjustment), Sodium citrate dihydrate (for pH-adjustment), α,α Trehalose dihydrate and Polysorbate 80.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines except those mentioned in **Section 6.6**.

6.3 Shelf life

4 years.

Reconstitution: After vial reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C-8 °C.

Infusion bag: After dilution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C-8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

Keep the vial in the original carton in order to protect from light. For storage conditions after reconstitution and dilution of the medicine, see **section 6.3.**

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 50 mg powder.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

General precautions

Procedures for proper handling and disposal of anticancer medicines should be considered.

Proper aseptic technique throughout the handling of **ADCETRIS** should be followed.

Instructions for reconstitution

Each single use vial must be reconstituted with 10,5 ml of water for injections to a final concentration of 5 mg/ml. Each vial contains a 10 % overfill giving 55 mg of ADCETRIS per vial and a total reconstituted volume of 11 ml.

1. Direct the stream toward the wall of the vial and not directly at the cake or powder.

2. Gently swirl the vial to aid dissolution. **DO NOT SHAKE**.

3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6,6.

4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicine.

Preparation of infusion solution

The appropriate amount of reconstituted **ADCETRIS** must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0,9 %) solution for injection in order to achieve a final concentration of 0,4-1,2 mg/ml **ADCETRIS**.

The recommended diluent volume is 150 ml. The already reconstituted **ADCETRIS** can also be diluted into 5 % dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing **ADCETRIS**.

DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements. Do not add other medicines to the prepared **ADCETRIS** infusion solution or intravenous infusion set.

The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0,9 %) solution for injection, 5 % dextrose for injection, or Lactated Ringer's for injection. Following dilution, infuse the **ADCETRIS** solution immediately at the recommended infusion rate or store the solution at 2–8 ˚C and use within 24 hours. DO NOT FREEZE.

Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

Determining dosage amount:

Calculation to determine the total* ADCETRIS *dose (ml) to be further diluted:

ADCETRIS dose (mg/kg) x patient's body weight (kg) = Total ADCETRIS dose Reconstituted vial concentration

(5 mg/ml) (ml) to be further diluted

Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximum recommended dose is 180 mg.

Calculation to determine the total number of* ADCETRIS *vials needed:

Total ADCETRIS dose (ml) to be administered = Number of ADCETRIS Total volume per vial (10 ml/vial)

vials needed

Table 4: Sample calculations for patients receiving the **recommended dose** of 1,8 mg/kg of **ADCETRIS** for weights ranging from 60 kg to 120 kg

Patient weight (kg)	**Total dose = patient weight multiplied by recommended dose (1,8 mg/kg[a])**	**Total volume to be diluted[b] = total dose divided by reconstituted vial concentration (5 mg/ml)**	**Number of vials needed total volume to be diluted divided by total volume per vial (10 mg/vial)**
60 kg	108 mg	21,6 ml	2,16 vials

80 kg	144 mg	28,8 ml	2,88 vials
100 kg	180 mg	36 ml	3,6 vials
120 kg[c]	180 mg[d]	36 ml	3,6 vials

[a] For a reduced dose, use 1,2 mg/kg for the calculation.

[b] To be diluted in 150 ml of diluent and administered by intravenous infusion over 30 min every 3 weeks.

[c] If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

[d] The maximal recommended dose is 180 mg.

Table 5: Sample calculations for patients receiving the recommended dose of 1,2 mg/kg of **ADCETRIS** for weights ranging from 60 kg to 120 kg as combination therapy or when a reduced dose is required

Patient weight (kg)	**Total dose = patient weight multiplied by recommended dose [1,2 mg/kg[a]])**	**Total volume to be diluted[b] = total dose divided by reconstituted vial concentration [5 mg/ml])**	**Number of vials needed = total volume to be diluted divided by total volume per vial [10 ml/vial])**
60 kg	72 mg	14,4 ml	1,44 vials
80 kg	96 mg	19,2 ml	1,92 vials
100 kg	120 mg	24 ml	2,4 vials
120 kg[c]	120 mg [d]	24 ml	2,4 vials

a. For a reduced dose, use 0.9 mg/kg for the calculation

b. To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.

c. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

d. The maximal recommended dose for combination therapy is 120 mg.

Disposal

ADCETRIS is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd

Building A,

Monte Circle

64 Montecasino Boulevard

Fourways

2191

South Africa

8. REGISTRATION NUMBER(S)

ADCETRIS: 480433

9. DATE OF PACKAGE INSERT FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

04 August 2020