אפריל 2019

**רופא/ה, רוקח/ת נכבד/ה,**

## הנדון: ADCETRIS® 50mg (brentuximab vedotin)
### עדכון בדבר תוספת התוויה לתכשיר ועדכון העלון לרופא

חברת טקדה ישראל בע"מ שמחה לעדכן כי משרד הבריאות אישר לאחרונה את הרחבת ההתוויה של התכשיר שבנדון.

נוסח תוספת ההתוויה כפי שאושר על-ידי משרד הבריאות הינו כדלקמן:

**ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.**

התוויה זו נוספת להתוויות הבאות הרשומות לתכשיר זה:

1. **ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):**
    1) **following autologous stem cell transplant (ASCT) or**
    2) **following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.**
2. **ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).**
3. **ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.**
4. **ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.**

מרכיב פעיל: **brentuximab vedotin 50mg/vial**

העלון לרופא של התכשיר שבנדון עודכן בהתאם. כמו כן, עדכון זה כולל עדכוני בטיחות (החמרות).

בעמודים הבאים מצויינים סעיפים בהם נעשה שינוי אשר מהווה החמרה או שינוי מהותי. למידע נוסף, יש לעיין בעלון לרופא המצורף כפי שאושר על ידי משרד הבריאות.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
http://www.old.health.gov.il/units/pharmacy/trufot/index.asp

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להלן פירוט השינויים העיקריים (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה):

בעלון לרופא:

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.

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### 4.2 Posology and method of administration

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**Posology**

**Previously Untreated 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 (G-CSF) is recommended for all patients with previously untreated HL receiving combination therapy beginning with the first dose (see section 4.4).

Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL.

**Table 1: Dosing recommendations for neutropenia**

| | **Monotherapy** | **Combination therapy**<br><br>Note: Primary prophylaxis with G-CSF is recommended for all patients receiving combination therapy beginning with the first dose. |
|---|---|---|
| **Severity grade of neutropenia**<br><br>**(signs and symptoms** [abbreviated description of CTCAE[a]]) | **Modification of dosing schedule** | **Modification of dosing schedule** |

| | | |
|---|---|---|
| Grade 1 (<LLN - 1500/$mm^3$<br><LLN - 1.5 x $10^9$/L) or<br>Grade 2 (<1500 - 1000/$mm^3$<br><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/$mm^3$<br><1.0 - 0.5 x $10^9$/L) or<br>Grade 4 (<500/$mm^3$<br><0.5 x $10^9$/L) | Withhold dose until toxicity returns to ≤ Grade 2 or<br>baseline then resume treatment at the same dose and schedule [b]. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for<br>patients who develop Grade 3<br>or Grade 4 neutropenia. | Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia. |

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

| | **Monotherapy** | **Combination therapy** |
|---|---|---|
| **Severity of peripheral sensory or motor neuropathy**<br>**(signs and symptoms** [abbreviated description of CTCAE[a]]) | **Modification of dose and schedule** | **Modification of dose and schedule** |
| Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function) | Continue with the same<br>dose and schedule | Continue with the same dose and schedule |
| Grade 2 (interfering with function but not<br>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 | Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks |
| Grade 3 (interfering with activities of<br>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 ADCETRIS until toxicity is ≤ Grade 2, then restart treatment at a reduced dose to 0.9 mg/kg every 2 weeks.. |

| | | |
|---|---|---|
| Grade 4 (sensory neuropathy which is disabling or motor neuropathy<br><br>that is life threatening or leads to<br><br>paralysis) | Discontinue treatment | Discontinue treatment |

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Special patient populations

*Renal and hepatic impairment*

Combination therapy

~~*Renal impairment*~~

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 renal impairment, where serum creatinine is ≥ 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is ≤ 40 mL/minute. Use of ADCETRIS in combination with chemotherapy should be avoided in patients with severe renal impairment.

Patients with hepatic impairment should be closely monitored for adverse events. The recommended starting dose in patients with mild hepatic impairment is 0.9 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. 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. Use of ADCETRIS in combination with chemotherapy should be avoided in patients with moderate and severe hepatic impairment.

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 ~~carefully~~ for adverse events (see section 5.2).

~~*Hepatic impairment*~~

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 ~~carefully~~ for adverse events (see section 5.2).

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**4.4 Special warnings and precautions for use**

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Febrile neutropenia

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In combination therapy with AVD, advanced age was a risk factor for febrile

neutropenia.When ADCETRIS is administered in combination with AVD, primary prophylaxis with G-CSF is recommended for all patients regardless of age beginning with the first dose.

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Sodium content in excipients

This medicinal product 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.

~~This medicinal product contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. To be taken into consideration for patients on a controlled sodium diet.~~

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

## 4.5 Interaction with other medicinal products and other forms of interaction

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Doxorubicin, vinblastine and dacarbazine (AVD)

The serum and plasma pharmacokinetic characteristics of ADC and MMAE respectively following administration of brentuximab vedotin in combination with AVD were similar to that in monotherapy.

Co-administration of brentuximab vedotin did not affect the plasma exposure of AVD.

Bleomycin

There were no formal drug-drug interaction studies with brentuximab vedotin and bleomycin(B). In a phase 1 dose finding and safety study (SGN35-009), unacceptable pulmonary toxicity (including 2 fatal events) was noted in 11 of 25 patients (44%) treated with brentuximab vedotin plus ABVD. No pulmonary toxicity or fatal events were reported with brentuximab vedotin + AVD. Therefore, co-administration of ADCETRIS with bleomycin is contraindicated (see section 4.2).

## 4.7 Effects on ability to drive and use machines

ADCETRIS ~~brentuximab vedotin~~ may have a moderate ~~minor~~ influence on the ability to drive and use machines (e.g. dizziness), see section 4.8.

## 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 (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) 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.

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Combination therapy

For safety information of chemotherapy agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine) for newly diagnosed patients with HL, refer to their summary of product characteristics.

In the study of ADCETRIS as combination therapy with AVD in 662 patients with previously untreated advanced HL (C25003), the most common adverse reactions (≥ 10%) were: neutropenia, nausea, constipation, vomiting, fatigue, peripheral sensory neuropathy, diarrhoea, pyrexia, alopecia, peripheral motor neuropathy, decreased weight, abdominal pain, anaemia, stomatitis, febrile neutropenia, bone pain, insomnia, decreased appetite, cough, headache, arthralgia, back pain, dyspnoea, myalgia, 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%).

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.

Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 3). Within each System Organ Class, adverse reactions are listed under frequency categories of: 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 the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 3: Adverse reactions to 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: | Herpes zoster, pneumonia, herpes simplex, oral candidiasis | Pneumonia, oral candidiasis, sepsis/septic shock, herpes simplex |
| Uncommon: | Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock | 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 |
| Uncommon: | Febrile neutropenia | |
| **Immune system disorders** | | |
| Uncommon: | Anaphylactic reaction | 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 | |
| Uncommon: | Demyelinating polyneuropathy | |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Very common: | Cough, dyspnoea | Cough, dyspnoea |
| **Gastro-intestinal disorders** | | |
| Very common: | Nausea, diarrhoea, 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 | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased |
| **Skin and subcutaneous tissue disorders** | | |
| Very common: | Rash[a], pruritus | Alopecia, rash[a] |
| Common: | Alopecia | Pruritus |
| Uncommon: | Stevens-Johnson syndrome/ toxic epidermal necrolysis | Stevens-Johnson syndrome[b] |
| **Musculoskeletal and connective tissue disorders** | | |
| Very common: | Arthralgia, myalgia | Bone pain, arthralgia, back pain, myalgia |
| Common: | Back pain | |

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| | | |
|---|---|---|
| **General disorders and administration site conditions** | | |
| Very common: | Fatigue, pyrexia, infusion-related reactions[a] | Fatigue, pyrexia |
| Common: | Chills | 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.

Description of selected adverse reactions

*Neutropenia and febrile neutropenia*

Monotherapy

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Combination therapy

In the clinical trial of ADCETRIS as combination therapy, neutropenia led to dose delays in 24% of patients. Grade 3 neutropenia was reported in 18% and Grade 4 neutropenia was reported in 47% of patients. Two percent of patients required dose reduction and < 1% discontinued one of more of the study drugs due to neutropenia.

Febrile neutropenia was reported in 21% of the patients who did not receive primary prophylaxis with G-CSF (see section 4.2). The frequency of febrile neutropenia was 11% in patients who received primary prophylaxis with G-CSF.

*Serious infections and opportunistic infections*

Monotherapy

In clinical trials, serious infections and opportunistic infections occurred in 10 % of patients sepsis or septic shock occurred in <1% of the patients. The most commonly reported opportunistic infections were herpes zoster and herpes simplex.

Combination therapy

In the clinical trial of ADCETRIS as combination therapy, serious infections including opportunistic infections occurred in 15% of patients; sepsis, neutropenic sepsis, septic shock or bacteraemia occurred in 4% of the patients. The most commonly reported opportunistic infections were herpes viral infections.

*Peripheral neuropathy*

Monotherapy

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Combination therapy

In the clinical trial of ADCETRIS as combination therapy, treatment emergent neuropathy occurred in 67% of the population; peripheral motor neuropathy occurred in 11% of patients. Peripheral neuropathy led to treatment discontinuation in 7%, dose reductions in 21%, and dose delays in 1% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 8 weeks. Patients who discontinued due to peripheral neuropathy received a median of 8 doses of ADCETRIS+AVD (A+AVD) before discontinuation of one or more agents.

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 91 weeks. At the time of last evaluation, most of the patients (76%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 10 weeks (ranged from 0 weeks to 139 weeks).

*Infusion-related reactions*

Monotherapy

*IRRs such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough were reported in 13 % of patients.*

*Anaphylactic reactions have been reported (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.*

Combination therapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough, infusion site pain and pyrexia were reported in 9% of patients. Anaphylactic reactions have been reported (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

*Immunogenicity*

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Elderly

*Monotherapy*

The safety profile in elderly patients was consistent with that of adult patients.

*Combination therapy*

In older patients (≥ 60 years of age; n=83 [13%]), the incidence of adverse events was similar across treatment arms. More serious adverse events and dose modifications (including dose delays, reductions, and discontinuations) were reported in the older patients compared with the overall study population. Advanced age was a risk factor for febrile neutropenia in patients in both arms. Older patients who received G-CSF primary prophylaxis had lower

incidence of neutropenia and febrile neutropenia than those who did not receive G-CSF primary prophylaxis.

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## 6.6 Special precautions for disposal and other handling

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Table 16: 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/kga]) | Total volume to be dilutedb = 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 kgc | 120 mg d | 24 mL | 2.4 vials |

For a reduced dose, use 0.9 mg/kg for the calculation..
To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
The maximal recommended dose for combination therapy is 120 mg.