יולי 2020

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 תוספת התוויה עבור 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 systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

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.**
5. **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.**

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 וניתן לקבלו מודפס על ידי פניה לחברת טקדה ישראל בע"מ, רח' אפעל 25, פתח תקוה, 03-3733140

בברכה,

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להלן פירוט השינויים העיקריים בעלון לרופא (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה, טקסט המהווה החמרה מודגש בצהוב):

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

…
Systemic anaplastic large cell lymphoma and Peripheral T-cell lymphomas (PTCL)

ADCETRIS is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.
…

4.2 Posology and method of administration

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Posology

Previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas

The recommended dose in combination with chemotherapy (cyclophosphamide [C], doxorubicin [H] and prednisone [P] [CHP]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for 6 to 8 cycles (see section 5.1).

Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients with previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas, receiving combination therapy (see section 4.4).

Refer to the SmPCs of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas.

…
Neutropenia

If neutropenia develops during treatment it should be managed by dose delays. See Table 1 and Table 2 ~~below~~ for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see also section 4.4).

Table 1: Dosing recommendations for neutropenia with monotherapy

	~~monotherapy~~	~~Combination therapy Note: Primary prophylaxis with G-CSF is recommended for all patients receiving combination therapy beginning with the first dose.~~
Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAEa])	Modification of dosing schedule	~~Modification of dosing schedule~~

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Grade 1 (<LLN - 1500/mm3 <LLN - 1.5 x 109/L) or Grade 2 (<1500 - 1000/mm3 <1.5 – 1.0 x 109/L)	Continue with the same dose and schedule.	~~Continue with the same dose and schedule.~~
Grade 3 (<1,000 - 500/mm3 <1.0 - 0.5 x 109/L) or Grade 4 (<500/mm3 <0.5 x 109/L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and scheduleb. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.	~~Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.~~

Table 2: Dosing recommendations for neutropenia during combination therapy

Severity grade of neutropenia **(signs and symptoms [abbreviated description of CTCAEa])**	**Modification of dosing schedule**
Grade 1 (< LLN-1500/mm3 **< LLN-1.5 x 109/L) or** **Grade 2 (< 1500-1000/mm3** **< 1.5-1.0 x 109/L)** **Grade 3 (< 1,000-500/mm3** **< 1.0-0.5 x 109/L) or** **Grade 4 (< 500/mm3** **< 0.5 x 109/L)**	**Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients receiving combination therapy. Continue with the same dose and schedule.**

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; see Neutrophils/granulocytes; LLN = lower limit of normal.

Peripheral neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table ~~2~~ 3 and 4 ~~below~~ for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see section 4.4).

Table ~~2~~3: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy with monotherapy

	~~monotherapy~~	~~Combination therapy~~
Severity of peripheral sensory or motor neuropathy (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 dose and schedule	~~Continue with the same dose and schedule~~
Grade 2 (interfering with function but not 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 up to a maximum of 120 mg every 3 weeks	~~reduced dose to 0.9 mg/ up to a maximum of 90 mg 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 up to a maximum of 120 mg every 3 weeks	~~Withhold treatment with ADCETRIS until toxicity ≤ Grade 2, then restart treatment at a reduced dose to 0.9 mg/ every 2 weeks~~
Grade 4 (sensory neuropathy ~~which~~ that 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.

Table 4: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy during combination therapy

	Combination therapy with AVD	Combination therapy with CHP
Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAEa])	**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 dose and schedule.	Continue with the same dose and schedule.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks.	Sensory neuropathy: Continue treatment at same dose level. Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks.
Grade 3 (interfering with activities of daily living)	Withhold treatment with ADCETRIS until toxicity is ≤ Grade 2, then restart treatment at a reduced dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks.	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue treatment.

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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) v4.03; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Special patient populations

Renal and hepatic impairment

Combination therapy

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Patients with hepatic impairment should be closely monitored for adverse events. The recommended starting dose in patients with mild hepatic impairment receiving ADCETRIS in combination with AVD is 0.9 mg/kg administered as an intravenous infusion over 30 minutes every ~~3~~2 weeks. The recommended starting dose in patients with mild hepatic impairment receiving ADCETRIS in combination with CHP is 1.2 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.

4.5 Interaction with other medicinal products and other forms of interaction

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Cyclophosphamide, Doxorubicin and Prednisone (CHP)

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

Co-administration of brentuximab vedotin is not expected to affect the exposure of CHP.

4.8 Undesirable effects

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Combination therapy

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

In the stud~~y~~ies of ADCETRIS as combination therapy ~~with AVD~~ in 662 patients with previously untreated advanced HL (C25003) and 223 patients with previously untreated CD30+ PTCL (SGN35-014), the most common adverse reactions (≥ 10%) were: infections, neutropenia, peripheral sensory neuropathy, nausea, constipation, vomiting, diarrhoea, fatigue, ~~peripheral sensory neuropathy, diarrhoea~~ pyrexia, alopecia, anaemia, ~~peripheral motor neuropathy, decreased weight~~ weight decreased, ~~abdominal pain, anaemia~~, stomatitis, febrile

neutropenia, abdominal pain, decreased appetite, insomnia, bone pain, ~~insomnia, decreased appetite~~ rash, cough, ~~headache~~, dyspnoea, arthralgia, myalgia, back pain, peripheral motor neuropathy, ~~dyspnoea, myalgia~~ upper respiratory tract infection, ~~alanine aminotransferase increased~~ and dizziness.

In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 3~~4~~6% of patients. Serious adverse reactions occurring in ≥ 3% of patients included febrile neutropenia (1~~7~~5%), pyrexia (5~~6~~%), and neutropenia (3%).

Adverse events led to treatment discontinuation in 10~~3~~% of patients. Adverse events that led to treatment discontinuation in ≥ 2% of patients included peripheral sensory neuropathy, and peripheral neuropathy ~~and peripheral motor neuropathy~~.

…

Table ~~3~~5: Adverse reactions to ADCETRIS

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy)
Infections and infestations		
Common:	Herpes zoster, pneumonia, herpes simplex, oral candidiasis	Pneumonia, oral candidiasis, sepsis/septic shock, herpes ~~simplex~~ zoster
Uncommon:	Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock	Herpes ~~zoster~~ simplex, Pneumocystis jiroveci pneumonia
…	…	…
Immune system disorders		
Uncommon:	Anaphylactic reaction	Anaphylactic transfusion reaction
Hepatobiliary disorders		
~~Very common:~~		~~Alanine aminotransferase (ALT) increased~~
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
…	…	…
Musculoskeletal and connective tissue disorders		
Very common:	Arthralgia, myalgia	Bone pain, arthralgia, myalgia, back pain, ~~myalgia~~
…	…	…

Description of selected adverse reactions

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Neutropenia and febrile neutropenia

Combination therapy

In the clinical trials of ADCETRIS as combination therapy, neutropenia led to dose delays in ~~24~~19% of patients. Grade 3 neutropenia was reported in 17~~8~~% and Grade 4 neutropenia was reported in 4~~17~~% 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 20~~1~~% of the patients who did not receive primary prophylaxis with G-CSF (see section 4.2). The frequency of febrile neutropenia was ~~11~~13% in patients who received primary prophylaxis with G-CSF.

...
Peripheral neuropathy
Combination therapy

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In the clinical trial of ADCETRIS as combination therapy with CHP, treatment emergent neuropathy occurred in 52% of the population; peripheral motor neuropathy occurred in 9% of patients. Peripheral neuropathy led to treatment discontinuation in 1%, dose reductions in 7% and dose delays in <1% of patients. For patients who experienced peripheral neuropathy the median time of onset was 9.1 weeks.

Patients who discontinued due to peripheral neuropathy received a median of 5 doses of ADCETRIS+CHP (A+CHP) 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 177 weeks. At the time of last evaluation, 64% 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 19.0 weeks (ranged from 0 weeks to 205 weeks).

Infusion-related reactions
...
Combination therapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough, infusion site pain and pyrexia were reported in 8~~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.

Elderly

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Combination therapy

In older patients (≥ 60 years of age; n = ~~83~~ 186 [~~13~~ 21%]), 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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5.2 Pharmacokinetic properties

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Combination therapy

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The pharmacokinetics of ADCETRIS in combination with CHP were evaluated in a single phase 3 study in 223 patients (SGN35-014). After multiple-dose IV infusion of 1.8 mg/kg ADCETRIS every 3 weeks, the pharmacokinetics of ADC and MMAE were similar to those of monotherapy.

6.6 Special precautions for disposal and other handling

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Table ~~16~~21: 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 kgc	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~~ 2 weeks as combination therapy with AVD or every 3 weeks when a reduced dose of the monotherapy is required.

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.

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