מאי 2022

רופא/ה, רוקח/ת נכבד/ה,

הנדון: ADCETRIS® 50mg (brentuximab vedotin)
עדכון העלון לרופא

חברת טקדה ישראל בע"מ מבקשת לידע כי העלון לרופא של התכשיר שבנדון עודכן לאחרונה.

התוויות 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.**
6. **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.**

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

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

4.4 Special warnings and precautions for use

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Severe cutaneous adverse reactions (SCARs)

~~Stevens-Johnson syndrome and toxic epidermal necrolysis~~

Cases of SCARs, including Stevens-Johnson syndrome (SJS) ~~and~~, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with ADCETRIS. Fatal outcomes have been reported for SJS and TEN. If SJS ~~or~~, TEN or DRESS occur, ADCETRIS should be discontinued and appropriate medical therapy should be administered.

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Infusion site extravasation

Extravasation during intravenous infusion has occurred. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

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4.8 Undesirable effects

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Table 5: Adverse reactions to ADCETRIS

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy)
Skin and subcutaneous tissue disorders		
Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS)	

a. Represents pooling of preferred terms.

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

c. Extravasation may result in related reactions include skin redness, pain, swelling, blistering, exfoliation, or cellulitis ~~sloughing~~ at or surrounding the infusion site.

Description of selected adverse reactions

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Immunogenicity

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Monotherapy Study C25002

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.

Combination Use Study C25004

The rate of ADA positivity was low in Study C25004; 4 patients (aged ≥ 12 years) of 59 patients became transiently ADA positive, and no patients became persistently ADA positive. Due to the small number of transiently ADA positive patients, the impact of ADA on efficacy is inconclusive.

Paediatric population

Monotherapy Study C25002

Safety was evaluated in a phase 1/2 study in paediatric patients aged 7-17 years of age (n = 36) with relapsed or refractory (r/r) HL and sALCL (see section 5.1). In this study in 36 patients, no new safety concerns were reported.

Combination Use Study C25004

Safety was evaluated in an open-label, multicenter trial in 59 paediatric patients aged

6-17 years of age with previously untreated advanced-stage classical CD30+ HL in combination with chemotherapy (see section 5.1). In this study, no new safety concerns were reported. The most common serious adverse reaction reported in this study was febrile neutropenia (17%). G-CSF prophylaxis was considered at the physician's discretion. Peripheral neuropathy events (per Standardized MedDRA Query) were reported in 24% of paediatric patients in this study.

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5.1 Pharmacodynamic properties

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Study SGN35-014

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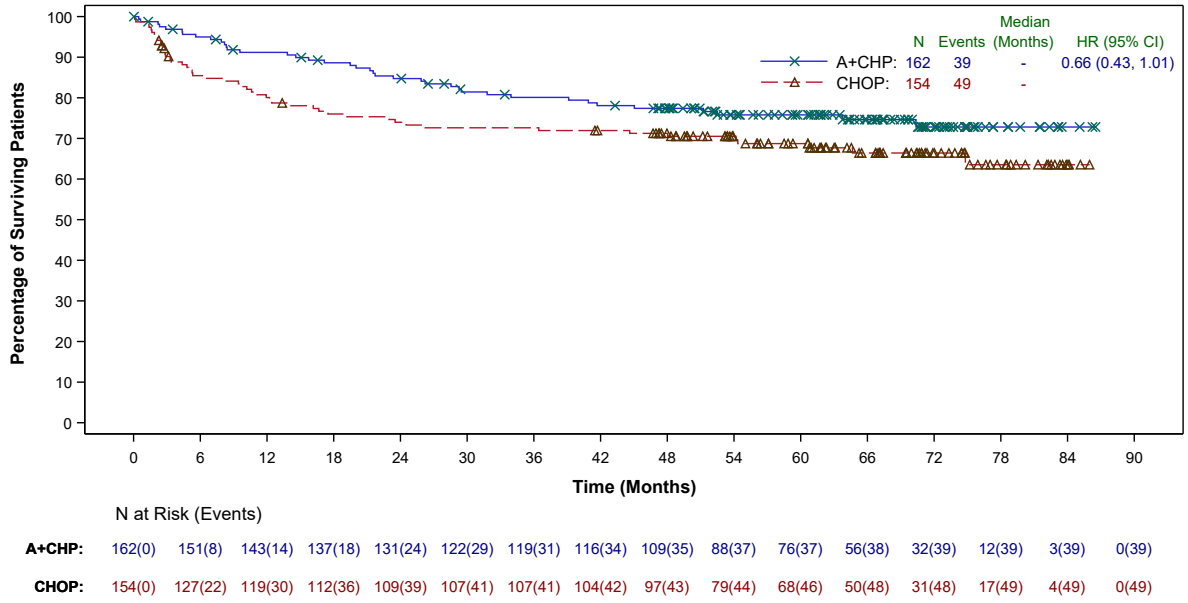
As of study closure more than 7 years after enrolment of the first patient, PFS per investigator results in the ITT population indicated a 30% reduction in the risk of a PFS event in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.70 [95% CI (0.53, 0.91)]). PFS per investigator results in the sALCL population indicated a 45% reduction in the risk of a PFS event in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.55 [95% CI (0.39, 0.79)]).

As of study closure, overall survival results continued to show a benefit and were consistent with those reported at the time of the primary analysis. Overall survival results in the ITT population indicated a 28% reduction in the risk of death in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.72 [95% CI (0.53 to 0.99)]). Overall survival results in the sALCL population indicated a 34% reduction in the risk of death in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.66 [95% CI (0.43, 1.01)]), see Figure 10.

Figure 10: Overall survival in the sALCL population (ADCETRIS + CHP vs. CHOP) (study closure)



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6.6 Special precautions for disposal and other handling

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Table 20: Sample calculations for patients receiving the recommended dose of 1.8 mg/kg, 1.2 mg/kg or 0.9 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg[a, b]

Recommended dose	Patient weight (kg)	Total dose = patient weight multiplied by recommended dose	Total volume to be diluted[c] = 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)
1.8 mg/kg (up to a maximum of 180 mg)	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[d]	180 mg	36 mL	3.6 vials
1.2 mg/kg (up to a maximum of 120 mg)	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[d]	120 mg	24 mL	2.4 vials
0.9 mg/kg (up to a maximum of 90 mg)	60 kg	54 mg	10.8 mL	1.08 vials
	80 kg	72 mg	14.4 mL	1.44 vials
	100 kg	90 mg	18 mL	1.8 vials
	120 kg[d]	90 mg	18 mL	1.8 vials

a. This table provides sample calculations for adult patients.
b. For paediatric patients studied in clinical trials (6-17 years of age), body surface area-based dosing was calculated as 48 mg/m^2 every two weeks in combination with AVD in a 28-day cycle or 72 mg/m^2 every three weeks as monotherapy. (See sections 5.1 and 5.2 for information on clinical studies conducted in paediatric patients.)
c. To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes.
d. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

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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,

אנה מורביוב
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