מארס 2018

**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 CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy**

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.**

**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 משמעותי. 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

ניתן 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 (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה):

**בעלון לרופא:**

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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**ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).**

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### 4.2 Posology and method of administration

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**Patients with CTCL should receive up to 16 cycles (see section 5.1).**

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*Paediatric population*

The safety and efficacy of children less than 18 years have not yet been established. ~~No data are available.~~ **Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.**

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### 4.4 Special warnings and precautions for use

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Peripheral neuropathy

Brentuximab vedotin treatment may cause peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases.

~~**In the pivotal phase 2 (SG035-0003 and SG035-0004) population, the incidence of pre-existing peripheral neuropathy was 24%. Treatment emergent neuropathy occurred in 56% of the population.**~~
~~**At the time of last evaluation, the majority of patients (83%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 17%, dose reductions were reported in 13%, and dose delays occurred in 21% of patients.**~~

~~**The incidence of pre-existing peripheral neuropathy in patients with relapsed or**~~

~~refractory HL or sALCL who were retreated with brentuximab vedotin was 48%. Treatment emergent neuropathy occurred in 69% of the population. At the time of last evaluation, the majority of patients who were retreated and experienced treatment emergent peripheral neuropathy (80%) had improvement or resolution of their peripheral neuropathy symptoms. Peripheral neuropathy led to discontinuation in 21% and dose modifications in 34% of patients who were retreated.~~

~~In the phase 3 population, at the time of last evaluation, the majority of patients in the brentuximab vedotin arm (85%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 23%, dose reductions were reported in 29%, and dose delays occurred in 22% of patients.~~

**In clinical trials, the majority of patients had improvement or resolution of their symptoms (see section 4.8)**. 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 a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment (see section 4.2).

…

**CD30+ CTCL**

**The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. In two single arm phase II studies of brentuximab vedotin, disease activity has been shown in the subtypes Sézary syndrome (SS), lymphomatoid papulosis (LyP) and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, Adcetris should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis (see section 5.1).**

…

## 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.

~~ADCETRIS was administered~~ **In the pooled dataset of Adcetris** as monotherapy ~~in 160 patients in two phase 2 studies in patients with relapsed or refractory~~ **across** HL**,** ~~or~~ 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.** ~~The median number of cycles was 9 in patients with relapsed or refractory HL and 7 in patients with relapsed or refractory sALCL.~~

~~ADCETRIS was also administered as monotherapy in 167 out of 329 patients in a randomized, placebo-controlled phase 3 study in patients with HL at increased risk of relapse or progression following ASCT. The median number of cycles received in both arms was 15.~~

~~Serious infections and opportunistic infections were very common in patients treated with this medicine (see section 4.4). In the phase 2 and the phase 3 population, the most commonly reported opportunistic infections were herpes zoster and herpes simplex.~~

~~Serious adverse drug reactions in the pivotal phase 2 and the phase 3 population were: pneumonia, acute respiratory distress syndrome, headache, neutropenia, thrombocytopenia, constipation, diarrhoea, vomiting, nausea, pyrexia, peripheral motor neuropathy, peripheral sensory neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.~~

~~The most frequently observed (≥20%) adverse reactions in the pivotal phase 2 and the phase 3 population were: peripheral sensory neuropathy , fatigue, nausea, diarrhoea, upper respiratory tract infection, neutropenia, and cough. In addition, adverse reactions also observed at ≥20% were vomiting and pyrexia in the phase 2 studies and peripheral motor neuropathy was also observed in the phase 3 population.~~

**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 ~~23% and 32~~ **24%** of patients receiving brentuximab vedotin. ~~in the phase 2 and the phase 3 population, respectively.Serious adverse reactions that led to treatment discontinuation in two or more patients in either the phase 2 or the phase 3 population were peripheral sensory neuropathy , peripheral motor neuropathy, demyelinating polyneuropathy, recurrent Hodgkin's disease, vomiting, and acute respiratory distress syndrome. Paresthesia also led to discontinuation in two or more patients in either the phase 2 or the phase 3 population.~~

**The safety data in patients retreated with ADCETRIS (SGN35-006, see section 5.1) 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 comb ned 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) (see section 5.1) were consistent with the safety profile of the pivotal clinical studies.

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).

Table 3: Adverse reactions to ADCETRIS

| System organ class | Adverse reactions |
|---|---|
| **Infections and infestations** | |
| Very common: | Infection[a], upper respiratory tract infection |
| Common: | ~~**Sepsis/septic shock**~~ Herpes zoster, pneumonia, herpes simplex**, oral candidiasis** |
| Uncommon: | ~~**Oral candidiasis,**~~ Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation**, sepsis/septic shock** |
| Frequency not known: | Progressive multifocal leukoencephalopathy |
| **Blood and lymphatic system disorders** | |
| Very common: | Neutropenia |
| Common: | Anaemia, thrombocytopenia |
| **Uncommon** ~~**Frequency not known:**~~ | Febrile neutropenia |
| **Immune system disorders** | |
| **Uncommon** ~~**Frequency not known:**~~ | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | |
| Common: | Hyperglycaemia |
| Uncommon: | Tumour lysis syndrome |
| **Nervous system disorders** | |
| Very common: | Peripheral sensory neuropathy, peripheral motor neuropathy |
| Common: | Dizziness~~**, demyelinating polyneuropathy**~~ |
| **Uncommon:** | **Demyelinating polyneuropathy** |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very Common: | Cough, dyspnoea |
| **Gastro-intestinal disorders** | |
| Very common: | **Nausea,** ~~**Diarrhoea**~~ **diarrhoea,** ~~**nausea,**~~ vomiting, constipation, abdominal pain |
| Uncommon: | Pancreatitis acute |
| **Hepatobiliary disorders** | |
| Common: | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | ~~**Alopecia**~~ **Rash**[a], pruritus |
| Common | ~~**Rash**~~ **Alopecia** |
| **Uncommon:** ~~**Rare:**~~ | Stevens-Johnson syndrome/ toxic epidermal necrolysis |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | **Arthralgia** ~~**Myalgia, arthralgia**~~ **myalgia** |
| Common: | Back pain |
| **General disorders and administration site conditions** | |
| Very common: | Fatigue, ~~**chills,**~~ pyrexia, infusion-related reactions[ba] |
| **Common:** | **Chills** |
| **Investigations** | |
| Very common: | Weight decreased |

~~[a] Preferred terms that were reported under the Infections and Infestations SOC~~

~~include sepsis/septic shock, upper respiratory tract infection, herpes zoster, and pneumonia.~~

~~b.~~ ~~Preferred terms associated with IRRs were headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough.~~

c. **Represents pooling of preferred terms.**

Description of selected adverse reactions

***Neutropenia***

**In clinical trials, neutropenia** led to dose delays in 14% ~~and 22%~~ of patients. ~~in the phase 2 and the phase 3 population, respectively.~~ **Grade 3 neutropenia was reported in 13% and Grade 4 neutropenia was reported in 5 % of patients. No patients required dose reduction or discontinued treatment for neutropenia.**

Severe and prolonged (≥1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. **Febrile neutropenia reported in <1% of the patients (see section 4.2).**

In the **pivotal** phase 2 population **(SG035-0003 and SG035-0004)**, the median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥7 days. Less than half of the patients in the pivotal phase 2 population with Grade 3 or Grade 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or Grade 2.

~~In the phase 3 population, Grade 3 neutropenia was reported in 22% of patients in the brentuximab vedotin arm and Grade 4 neutropenia was reported in 7% of patients in the brentuximab vedotin arm. No patients required dose reduction or discontinued treatment for neutropenia.~~

***Serious infections and opportunistic infections***

In ~~the phase 3 population~~ **clinical trials,** serious infections **and opportunistic infections occurred in 10 %** ~~were reported in 9%~~ of patients ~~in the brentuximab vedotin arm. No events of bacteraemia,~~ sepsis or septic shock **occurred in <1% of the patients.** ~~were reported in the brentuximab vedotin arm.~~
**The most commonly reported opportunistic infections were herpes zoster and herpes simplex.**

***Peripheral neuropathy***

~~Peripheral sensory neuropathy led to dose delays in 13% and 16%~~ **In clinical trials treatment emergent neuropathy occurred in 59%** of ~~patients in the phase 2 and the phase 3~~ **the population**~~, respectively. In addition,~~ peripheral motor neuropathy **occurred in 14% of patients. Peripheral neuropathy led to treatment discontinuation in 15%, dose reductions in 15%, and** ~~and upper respiratory tract infection both led to~~ dose delays in ~~6~~ **17**% of patients ~~in the phase 3 population~~.

**For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 12 weeks. The median duration of treatment for patients who discontinued due to peripheral neuropathy was 12 cycles.**

~~Peripheral sensory neuropathy led to dose reductions in 9% and 22% of patients in the~~

~~phase 2 and the phase 3 population, respectively. In addition, peripheral motor neuropathy also led to dose reductions in 6% of patients in the phase 3 population. Ninety percent (90%) and sixty eight percent (68%) of patients in the phase 2 population and the phase 3 population, respectively, remained at the recommended dose of 1.8 mg/kg while on treatment.~~

Among patients who experienced peripheral neuropathy in the **pivotal** phase 2~~ population~~ **studies (SG035-0003 and SG035-0004) and randomized phase 3 studies (SGN35-005 and C25001)**, the median follow up time from end of treatment until last evaluation ~~was approximately~~ **ranged from** 48.9 **to 98** weeks. At the time of last evaluation, **most** ~~83%~~ of the ~~89~~ patients **(82-85%)** who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement for all events ~~was 16 weeks~~ ~~(~~ranged from ~~0.3~~ **16** ~~weeks~~ to ~~106.6~~**23.4** weeks~~)~~.

**In** ~~Among~~ patients **with relapsed or refractory HL or sALCL** ~~who experienced peripheral neuropathy in the phase 3 population, the median follow up time from end of treatment until last evaluation was approximately 98 weeks. At the time of last evaluation, 85% of patients who experienced peripheral neuropathy in the~~ **who were retreated with** brentuximab vedotin ~~arm experienced resolution or~~ **(SGN35-006), the majority of patients (80%) also had** improvement **or resolution** of their peripheral neuropathy symptoms **at the time of last evaluation.**
~~Overall, the median time to resolution or improvement of peripheral neuropathy events in the brentuximab vedotin arm was 23.4 weeks (range from 0.1 weeks to 138.3 weeks).~~

***Infusion-related reactions***

IRRs~~ were reported in 11% and 15% of patients in the phase 2 and the phase 3 population, respectively. In either the phase 2 population or the phase 3 population, the adverse events most commonly associated with IRRs were mild to moderate (Grade 1 or Grade 2) and included~~ **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.

~~Febrile neutropenia has been reported (see section 4.2). A patient enrolled in a phase 1 dose escalation trial experienced Grade 5 febrile neutropenia after receiving a single dose of 3.6 mg/kg of brentuximab vedotin.~~

Immunogenicity

~~Patients with relapsed or refractory HL or sALCL in two pivotal phase 2 studies were~~ **In clinical trials, patients were periodically** tested for antibodies to brentuximab vedotin ~~every 3 weeks~~ using a sensitive electrochemiluminescent immunoassay. ~~Patients with HL at increased risk of relapse or progression following ASCT in the phase 3 study were also tested. Approximately 7% of patients in the phase 2 studies and 6% of~~ **There was a higher incidence of infusion-related reactions observed in** patients ~~in the brentuximab vedotin arm of the phase 3 study developed~~ **with** ~~persistently positive anti-drug~~ antibodies ~~(ADA)~~ **to brentuximab vedotin relative to patients who tested transiently positive or negative.** ~~Two patients in the phase 2 studies and two patients in the phase 3~~

~~study experienced adverse reactions consistent with IRRs that led to discontinuation of treatment.~~

The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin. ~~While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive ADA relative to patients with transiently positive ADA and never positive ADA.~~
**While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive anti-drug antibodies (ADA) relative to patients with transiently positive ADA and never positive ADA.**
**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.**

**Paediatric population**

**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.**

~~**Retreatment**~~

~~**Retreatment with ADCETRIS was administered in 21 patients with relapsed or refractory HL and 8 patients with relapsed sALCL. The median number of cycles was 7 (range, 2 to 37 cycles) (see section 5.1). The types and rates of adverse reactions reported for 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 1 or 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.**~~