Gilead Sciences Israel Ltd.
4 HaHarash Street, Hod Hasharon
Tel: 972-8802050

אפריל 2023

עדכון עלון לרופא ולצרכן לתכשיר:

Yescarta®

Cells dispersion for intravenous infusion

(axicabtagene ciloleucel)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם על עדכון עלונים לתכשיר בנדון.

ההתוויה הרשומה לתכשיר בישראל:

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy .

Limitation of Use: Yescarta is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות https://israeldrugs.health.gov.il/#!/byDrug/drugs/index.html.

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל

התכשיר זמין בכל קופות החולים.

בברכה,

מאיה מלל

רוקחת ממונה, גיליאד סיאנסז ישראל בע"מ

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העדכונים המהותיים בעלון לרופא:

4.1 Therapeutic indications

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Limitation of Use: Yescarta is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

4.8 Undesirable effects

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Follicular lymphoma

The safety of Yescarta was evaluated in ZUMA-5, a study that included 146 patients with r/r iNHL (of which 124 patients had r/r FL) who received CD19-positive CAR T cells. Patients with a history of CNS disorders or autoimmune disease requiring systemic immunosuppression were ineligible. The median age was 61 years (range: 34 to 79 years), 43% were female, 93% were white, 3% were black, and 1% were Asian.

The most common non-laboratory adverse reactions (incidence ≥ 20%) included fever, CRS, hypotension, encephalopathy, fatigue, headache, infections with pathogen unspecified, tachycardia, febrile neutropenia, musculoskeletal pain, nausea, tremor, chills, diarrhoea, constipation, decreased appetite, cough, vomiting, hypoxia, arrhythmia, and dizziness. Serious adverse reactions occurred in 48% of patients. Serious adverse reactions in > 2% of patients included febrile neutropenia, encephalopathy, fever, CRS, infections with pathogen unspecified, pneumonia, hypoxia, and hypotension.

The most common (≥ 10%) Grade 3 or higher reactions included febrile neutropenia, encephalopathy, and infections with pathogen unspecified. Fatal adverse reactions occurred in 1% of patients and included CRS and fungal infection.

Fifty-one percent (75/146) of patients received tocilizumab after infusion of Yescarta.

In addition, safety data is presented below -from a subset of 119 patients with r/r FL only from the 24-month follow-up analysis where the median actual duration of follow-up was 25.9 months (range: 0.3 to 44.3 months).

For this 24-month analysis, the most significant and frequently occurring adverse reactions were CRS (77%), infections (59%), and encephalopathy (47%).

Serious adverse reactions occurred in 45% of patients. The most common (≥ 5%) serious adverse reactions included encephalopathy (16%), unspecified pathogen infections (12%), CRS (12%), and bacterial infection (5%).

The most common (≥ 5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (14%), unspecified pathogen infections (11%), CRS (6%), and bacterial infection (5%). The most common

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Grade 3 or higher haematological adverse reactions included lymphopenia (99%), leukopenia (94%), neutropenia (92%), thrombocytopenia (34%), and anaemia (33%).

5.1 Pharmacodynamic properties

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Relapsed or refractory FL (ZUMA-5)

Efficacy in FL is based on a single-arm, open-label, multicenter trial (ZUMA-5) that evaluated a single infusion of Yescarta in adult patients with r/r FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or any history of CNS lymphoma or CNS disorders. Following lymphodepleting chemotherapy, Yescarta was administered as a single intravenous infusion with a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the fifth, fourth, and third day before Yescarta.

Of 123 patients with FL who underwent leukapheresis, 120 received Yescarta. Of the remaining three patients (2%) who were not treated, one was ineligible due to thrombocytopenia, one went into remission prior to initiating lymphodepletion, and one died of cardiac arrest. There were no manufacturing failures. Of the 120 patients with FL infused with Yescarta, the 81 consecutive patients included in the primary efficacy analysis had at least 9 months of potential follow-up from date of first response.

Among the 81 patients with FL included in the primary efficacy analysis, the median age was 62 years (range: 34 to 79 years), 46% were female, 93% were white, 4% were black, and 3% were Asian. The median number of prior systemic therapies was 3 (range: 2 to 9), with 32% having 2 prior lines, 22% having 3 prior lines, and 46% having ≥ 4 prior lines. Thirty-one percent had received a PI3K inhibitor, 72% had progression within 6 months of the most recent regimen, and 56% had progression within 24 months of initiating their first anti-CD20 combination therapy. Between leukapheresis and administration of Yescarta, one patient (1%) in the primary efficacy analysis received bridging therapy.

Among the 81 patients included in the primary efficacy analysis, the median time from leukapheresis to product delivery was 17 days (range: 13 to 33 days) and leukapheresis to product infusion was 27 days (range: 19 to 250 days). The median dose of Yescarta was 2.0×10^6 CAR T cells/kg (range 1.3 to 2.1 $\times 10^6$ CAR T cells/kg). All treated patients received Yescarta infusion on day 0 and were hospitalized until at least day 7.

Efficacy was established on the basis of objective response rate and DOR as determined by an independent review committee (Table 6 and Table 7). The median time to response in the primary efficacy population was 1.0 month (range: 0.8 to 3.1 months).

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Table 6. Response Rate in Patients with Relapsed or Refractory FL in ZUMA-5

	Primary Efficacy Analysis (N = 81)	All Leukapheresed Patients (N = 123)
Objective Response Rate[a], n (95% CI)	74 (91%) (83, 96)	110 (89%) (83, 94)
Complete Remission[b], n (95% CI)	49 (60%) (49, 71)	76 (62%) (53, 70)
Partial Remission, n (95% CI)	25 (31%) (21, 42)	34 (28%) (20, 36)

CI, confidence interval.
a. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the independent review committee.
b. Complete remission required documentation of a negative bone marrow biopsy after treatment, in patients who did not have a negative bone marrow biopsy between their most recent disease progression prior to ZUMA-5 and initiation of lymphodepleting chemotherapy.

Table 7. Duration of Response in Patients with Relapsed or Refractory FL in ZUMA-5

	From N of 81
Number of Responders	74
DOR (Months)[a]	
Median[b]	NE
(95% CI)	(20.8, NE)
Range[c]	0.0, 25.0+
Rate of Continued Remission[a, b, d]	
At 12 months (95% CI), %	76.2 (63.9, 84.7)
At 18 months (95% CI), %	74.2 (61.5, 83.2)
Median Follow-up for DOR (Months)[a, b]	14.5

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.
a. Among all responders in the primary efficacy population. DOR is measured from the date of first objective response to the date of progression or death from any cause.
b. Kaplan-Meier estimate.
c. A "+" sign indicates a censored value.
d. Measured from the date of first objective response to the date of progression or death.

העדכונים המהותיים בעלון לצרכן:

למה מיועדת התרופה?

יסקרטה מיועדת לטיפול במבוגרים הסובלים מלימפומה מפושטת של תאי B גדולים (DLBCL) ולימפומה של תאי B בדרגת ממאירות גבוהה (HGBL) אשר עמידה בפני, או נשנתה תוך 12 חודשים מסיום טיפול כימואימונותרפי בקו ראשון.

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יסקרטה מיועדת לטיפול במבוגרים עם מחלה חוזרת או עמידה הסובלים מלימפומה מפושטת של תאי B גדולים (DLBCL) ולימפומה ראשונית מיצרית של תאי B גדולים (PMBCL), לאחר שני קווי טיפול מערכתיים או יותר.

הגבלות שימוש: יסקרטה אינה מיועדת לטיפול בחולים עם לימפומה ראשונית או שניונית של מערכת העצבים.

יסקרטה מיועדת לטיפול במבוגרים עם מחלה חוזרת או עמידה הסובלים מלימפומה זקיקית (FL) לאחר שני קווי טיפול מערכתיים או יותר.

קבוצה תרפויטית: תרופות אנטיאופלסטיות אחרות.

יסקרטה הינה תכשיר מסוג תרפיה גנטית המיועדת לטיפול במבוגרים עם לימפומה אגרסיבית מפושטת של תאי B גדולים (DLBCL) ~~ובלימפומה~~, בלימפומה ראשונית מיצרית של תאי B גדולים (PMBCL) ובלימפומה זקיקית (FL) המשפיעות על רקמת הלימפה שלך (חלק ממערכת החיסון) אשר משפיעה על סוג מסויים של תאי דם לבנים הנקראים לימפוציטים מסוג B ועל איברים אחרים בגופך. כמות גדולה מדי של תאים לבנים לא תקינים אלו מצטברת ברקמה שלך, מה שעלול לגרום לתסמינים שאתה עשוי לחוות. ~~התכשיר מיועד לטפל במצבים אלו כאשר התרופות האחרות שקיימות חדלו מלהשפיע עליך.~~