נובמבר 2021

הנדון: **תוספת התוויה – Lupus nephritis**

Benlysta 200 mg
בנליסטה 200 מ"ג

Solution for injection in pre-filled pen
תמיסה להזרקה בעט מזרק מוכן לשימוש

מרכיבים פעילים וחוזקם:

Belimumab 200 mg/1 ml

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על תוספת התוויה – לופוס נפריטיס (Lupus nephritis) ועל עדכון העלונים לרופא ולצרכן של התכשיר בנליסטה 200 בעקבות זאת.

בהודעה זו מצוינים העדכונים המהותיים בלבד.
מקרא לעדכונים המסומנים:
תוספת – כתב **כחול**; תוספת החמרה – כתב **כחול** – מסומן בצהוב מרקר; מידע שהוסר – מסומן בקו אדום חוצה ~~XXX~~

התוויה חדשה - SPC:	התוויה נוכחית - SPC:
Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1). Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1). Limitations of Use: The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system lupus. Benlysta has not been studied in combination with other biologics. Use of Benlysta is not recommended in these situations.	Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

עדכונים מהותיים שנעשו בעלון לרופא:

4.1 Therapeutic indications

Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).

Limitations of Use: The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system lupus. Benlysta has not been studied in combination with other biologics. Use of Benlysta is not recommended in these situations.

4.2 Posology and method of administration

SLE
The recommended dose is 200 mg once weekly, administered subcutaneously. Dosing is not based on weight (see section 5.2).

The patient's condition should be evaluated continuously. Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment.

Lupus nephritis
In patients initiating therapy with Benlysta for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with Benlysta for active lupus nephritis, the recommended dosage is 200 mg once weekly. Benlysta should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. The patient's condition should be evaluated continuously.

Missed doses
If a dose is missed, it should be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration, or start a new weekly schedule from the day that the missed dose was administered. ~~It is not necessary to administer two doses on the same day.~~

Changing the weekly dosing day
If patients wish to change their weekly dosing day, a new dose can be given on the newly preferred day of the week. Thereafter the patient should continue with the new weekly schedule from that day, even if the dosing interval may be temporarily less than a week.

Transition from intravenous to subcutaneous administration
SLE
If a patient with SLE is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first subcutaneous injection should be administered 1 to 4 weeks after the last intravenous dose (see section 5.2).

Lupus nephritis
If a patient with lupus nephritis is being transitioned from Benlysta intravenous administration to subcutaneous administration, the first dose of 200 mg subcutaneous injection should be administered 1 to 2 weeks after the last intravenous dose. This transition should occur any time after the patient completes the first 2 intravenous doses (see section 5.2).

(…)

Method of administration
The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only. The recommended injection sites are the abdomen or thigh. When injecting in the same region, patients should be advised to use a different injection site for each ~~week~~injection; injections should never be given into areas where the skin is tender, bruised, red, or hard. When a 400 mg dose is administered at the same site, it is recommended that the 2 individual 200 mg injections are administered at least 5 cm (approximately 2 inches) apart.
(…)

4.4 Special warnings and precautions for use
(…)
Benlysta has not been studied in the following adult and paediatric patient groups, and is not recommended in:

- severe active central nervous system lupus (see section 5.1)
- ~~severe active lupus nephritis (see section 5.1)~~
- HIV
- a history of, or current, hepatitis B or C
- hypogammaglobulinaemia (IgG <400 mg/dl) or IgA deficiency (IgA <10 mg/dl)
- a history of major organ transplant or hematopoietic stem cell /marrow transplant or renal transplant.

Concomitant use with B cell targeted therapy ~~or cyclophosphamide~~
Benlysta has not been studied in combination with other B cell targeted therapy ~~or intravenous cyclophosphamide~~. Caution should be exercised if Benlysta is co-administered with other B cell targeted therapy ~~or cyclophosphamide~~.
(…)

4.8 Undesirable effects
(…)
Summary of the safety profile in adults

The safety of belimumab in patients with SLE has been evaluated in 3 pre-registration~~,~~ placebo-controlled intravenous studies, 1 placebo-controlled subcutaneous study, and one post-marketing~~,~~ placebo-controlled intravenous study~~,~~ the safety in patients with active lupus nephritis has been evaluated in one placebo-controlled intravenous study.

The data presented in the table below reflect exposure ~~to Benlysta~~ in 674 patients with SLE administered ~~(10 mg/kg~~Benlysta intravenously (10 mg/kg over a 1-hour period on Days 0, 14, 28, and then every 28 days for up to 52 weeks~~) in 674 patients with SLE, including 472 exposed for at least 52 weeks,~~), and 556 patients with SLE exposed to ~~200 mg~~ Benlysta subcutaneously (200 mg once weekly ~~for~~ up to 52 weeks~~.~~). The safety data presented include data beyond Week 52 in some patients~~.~~ with SLE. The data reflect additional exposure in 224 patients with active lupus nephritis who received Benlysta intravenously (10 mg/kg for up to 104 weeks). Data from post-marketing reports are also included.

(…)

The most frequently reported adverse reactions (>5% of patients with active lupus nephritis treated with Benlysta plus standard of care) were upper respiratory tract infection, urinary tract infection, and herpes zoster. The proportion of patients who discontinued treatment due to adverse reactions was 12.9% for Benlysta-treated patients and 12.9% for placebo-treated patients.

(…)

Description of selected adverse reactions

(…)

Infections:

In the lupus nephritis study, patients were receiving a background of standard therapy (see section 5.1) and the overall incidence of infections was 82% in patients receiving Benlysta compared with 76% in patients receiving placebo. Serious infections occurred in 13.8% of patients receiving Benlysta and in 17.0% of patients receiving placebo. Fatal infections occurred in 0.9% (2/224) of patients receiving Benlysta and in 0.9% (2/224) of patients receiving placebo.

(…)

5.1 Pharmacodynamic properties

(…)

Pharmacodynamic effects

(…)

In patients with active lupus nephritis, following treatment with Benlysta (10 mg/kg intravenously) or placebo, there was an increase in serum IgG levels which was associated with decreased proteinuria. Relative to placebo, smaller increases in serum IgG levels were observed in the Benlysta group as expected with the known mechanism of belimumab. At Week 104, the median percent increase from baseline in IgG was 17% for Benlysta and 37% for placebo. Reductions in autoantibodies, increases in complement, and reductions in circulating total B cells and B-cell subsets observed were consistent with the SLE studies.

(…)

Immunogenicity

(…)

In the lupus nephritis study where 224 patients received Benlysta 10 mg/kg intravenously, no anti-belimumab antibodies were detected.

(…)

Clinical efficacy and safety

(…)

Lupus nephritis

Subcutaneous injection

The efficacy and safety of Benlysta 200 mg administered subcutaneously to patients with active lupus nephritis is based on data from administration of Benlysta 10 mg/kg intravenously and pharmacokinetic modelling and simulation (see section 5.2).

In the subcutaneous SLE study, described above, patients who had severe active lupus nephritis were excluded; however, 12% of patients had renal organ domain involvement at baseline (based on SELENA SLEDAI assessment). The following study in active lupus nephritis has been conducted.

Intravenous infusion

The efficacy and safety of Benlysta 10 mg/kg administered intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days, were evaluated in a 104-week randomised (1:1), double-blind, placebo-controlled, Phase III study (BEL114054) in 448 patients with active lupus nephritis. The patients had a clinical diagnosis of SLE according to ACR classification criteria, biopsy proven lupus nephritis Class III, IV, and/or V and had active renal disease at screening requiring standard therapy. Standard therapy included corticosteroids, 0 to 3 intravenous administrations of methylprednisolone (500 to1000 mg per administration), followed by oral prednisone 0.5 to1 mg/kg/day with a total daily dose ≤60 mg/day and tapered to ≤10 mg/day by Week 24, with:

- mycophenolate mofetil 1 to 3 g/day orally or mycophenolate sodium 720 to 2160 mg/day orally for induction and maintenance, or

- cyclophosphamide 500 mg intravenously every 2 weeks for 6 infusions for induction followed by azathioprine orally at a target dose of 2 mg/kg/day for maintenance.

This study was conducted in Asia, North America, South America, and Europe. Patient median age was 31 years (range: 18 to 77 years); the majority (88%) were female.

The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at Week 104 defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: urinary protein:creatinine ratio (uPCR) ≤700 mg/g (79.5 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 or no decrease in eGFR of >20% from pre-flare value.

The major secondary endpoints included:

- Complete Renal Response (CRR) defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: uPCR <500 mg/g (56.8 mg/mmol) and eGFR ≥90 mL/min/1.73m^2 or no decrease in eGFR of >10% from pre-flare value.
- PERR at Week 52.
- Time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined as increased proteinuria, and/or impaired renal function], or receipt of renal disease-related prohibited therapy).

For PERR and CRR endpoints, steroid treatment had to be reduced to ≤10 mg/day from Week 24 to be considered a responder. For these endpoints, patients who discontinued treatment early, received prohibited medication, or withdrew from the study early were considered non-responders.

The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving Benlysta compared with placebo. The major secondary endpoints also showed significant improvement with Benlysta compared with placebo (Table 3).

Table 3: Efficacy results in adult patients with lupus nephritis

Efficacy Endpoint	Placebo N=223	Benlysta 10 mg/kg N=223	Observed difference vs. placebo	Odds/Hazard ratio vs. placebo (95% CI)	P-value
PERR at Week 1041 Responders	32.3%	43.0%	10.8%	OR 1.55 (1.04, 2.32)	0.0311
Components of PERR					
Urine protein: creatinine ratio ≤700 mg/g (79.5 mg/mmol)	33.6%	44.4%	10.8%	OR 1.54 (1.04, 2.29)	0.0320
eGFR≥60 mL/min/1.73m2 or no decrease in eGFR from pre-flare value of >20%	50.2%	57.4%	7.2%	OR 1.32 (0.90, 1.94)	0.1599
Not treatment failure[3]	74.4%	83.0%	8.5%	OR 1.65 (1.03, 2.63)	0.0364
CRR at Week 1041 Responders	19.7%	30.0%	10.3%	OR 1.74 (1.11, 2.74)	0.0167
Components of CRR					
Urine protein: creatinine ratio <500 mg/g (56.8 mg/mmol)	28.7%	39.5%	10.8%	OR 1.58 (1.05, 2.38)	0.0268
eGFR≥90 mL/min/1.73m^2 or no decrease in eGFR from pre-flare value of >10%	39.9%	46.6%	6.7%	OR 1.33 (0.90, 1.96)	0.1539
Not treatment failure[3]	74.4%	83.0%	8.5%	OR 1.65 (1.03, 2.63)	0.0364

Efficacy Endpoint	Placebo N=223	Benlysta 10 mg/kg N=223	Observed difference vs. placebo	Odds/Hazard ratio vs. placebo (95% CI)	P-value
PERR at Week 52[1] Responders	35.4%	46.6%	11.2%	OR 1.59 (1.06, 2.38)	0.0245
Time to Renal-Related Event or Death[1] Percentage of patients with event[2]	28.3%	15.7%	-		
Time to event [Hazard ratio (95% CI)]			-	HR 0.51 (0.34, 0.77)	0.0014

[1]PERR at Week 104 was the primary efficacy analysis; CRR at Week 104, PERR at Week 52 and time to renal-related event or death were included in the pre-specified testing hierarchy.
[2]When excluding deaths from the analysis (1 for Benlysta; 2 for placebo), the percentage of patients with a renal-related event was 15.2% for Benlysta compared with 27.4% for placebo (HR = 0.51; 95% CI: 0.34, 0.78).
[3]Treatment failure: Patients who took protocol-prohibited medication.

A numerically greater percentage of patients receiving Benlysta achieved PERR beginning at Week 24 compared with placebo, and this treatment difference was maintained through to Week 104. Beginning at Week 12, a numerically greater percentage of patients receiving Benlysta achieved CRR compared with placebo and the numerical difference was maintained through to Week 104 (Figure 2).

Figure 2. Response Rates in Adults with Lupus Nephritis by Visit
(see in the leaflet)
Figure 3. Odds Ratio of PERR and CRR at Week 104 across Subgroups
(see in the leaflet)

5.2 Pharmacokinetic properties
Lupus nephritis study
A population pharmacokinetic analysis was conducted in 224 adult patients with lupus nephritis who received Benlysta 10 mg/kg intravenously (Days 0, 14, 28, and then every 28 days up to 104 weeks). In patients with lupus nephritis, due to renal disease activity, belimumab clearance was initially higher than observed in SLE studies; however, after 24 weeks of treatment and throughout the remainder of the study, belimumab clearance and exposure were similar to that observed in adult patients with SLE who received Benlysta 10 mg/kg intravenously.

Based on population pharmacokinetic modelling and simulation, the steady-state average concentrations of subcutaneous administration of belimumab 200 mg once weekly in adults with lupus nephritis are predicted to be similar to those observed in adults with lupus nephritis receiving belimumab 10 mg/kg intravenously every 4 weeks.

(…)
Transitioning from intravenous to subcutaneous administration
(…)
Lupus nephritis
One to 2 weeks after completing the first 2 intravenous doses, patients with lupus nephritis transitioning from 10 mg/kg intravenously to 200 mg subcutaneously weekly, are predicted to have average belimumab serum concentrations similar to patients dosed with 10 mg/kg intravenously every 4 weeks based on population PK simulations (see section 4.2).
(…)

6.4 Special precautions for storage
Store in a refrigerator (2°C to 8°C) Until 30 minutes before use.
Do not freeze.
Store in the original carton in order to protect from light.
~~Do not use if left out at room temperature more than 12 hours.~~
A single Benlysta pre-filled syringe or pre-filled pen can be stored at temperatures up to a maximum of 25°C for a period of up to 12 hours. The syringe or pen must be protected from light, and discarded if not used within the 12 hour period.
Do not Shake.
(…)

עדכונים מהותיים שנעשו בעלון לצרכן:

1. למה מיועדת התרופה?

~~**בנליסטה 200 מ"ג היא תרופה המשמשת לטיפול בזאבת (לופוס)** אדמנתית מערכתית (SLE), במבוגרים (מגיל 18 ומעלה), שמחלתם עדיין מאוד פעילה למרות הטיפול הרגיל.~~

בנליסטה 200 מ"ג מיועדת כתוספת טיפול במטופלים מבוגרים עם זאבת (לופוס) אדמנתית מערכתית (SLE) פעילה, חיובית לנוגדנים אוטואימוניים, עם רמת פעילות גבוהה של המחלה (למשל נוכחות נוגדנים נגד דנ"א דו גדילי (dsDNA) ורמת משלים נמוכה (low complement)) למרות הטיפול הרגיל.

בנליסטה מיועדת לטיפול במטופלים מבוגרים עם זאבת (לופוס) נפריטיס פעילה בשילוב עם טיפולים מדכאי מערכת חיסון.

2. לפני שימוש בתרופה

(...)

אזהרות מיוחדות הנוגעות לשימוש בתרופה

לפני הטיפול בבנליסטה, ספר לרופא אם:

(...)

- **הזאבת שלך משפיעה ~~על הכליות או~~ על מערכת העצבים שלך.**

(...)

אינטראקציות/תגובות בין תרופתיות:

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד אם אתה לוקח תרופות המשפיעות על מערכת החיסון:

~~- ציקלופוספאמיד (תרופה המשמשת לטיפול במספר סוגי סרטן ומחלות אוטואימוניות)~~

(...)

3. כיצד תשתמש בתרופה?

(...)

בנליסטה 200 מ"ג ניתנת בזריקה מתחת לעור שלך באותו היום בכל שבוע.

המינון ואופן הטיפול יקבעו על-ידי הרופא בלבד.

זאבת (לופוס) אדמנתית מערכתית (SLE)

המינון המקובל בדרך כלל הוא: 200 מ"ג (תכולה מלאה של עט אחד) פעם בשבוע~~, בזריקה מתחת לעור שלך באותו היום בכל שבוע~~.

זאבת (לופוס) נפריטיס

המינון המקובל עשוי להשתנות. הרופא שלך יקבע את המינון הנכון בשבילך, שהוא:

- מנה של 200 מ"ג (תוכן מלא של עט אחד) פעם בשבוע.

או

- מנה של 400 מ"ג (תוכן מלא של שני עטים בפעם אחת) פעם בשבוע למשך 4 שבועות. בהמשך, המינון המומלץ הוא 200 מ"ג (תוכן מלא של עט אחד) פעם בשבוע.

(...)

5. איך לאחסן את התרופה?

(...)

יש לאחסן במקרר (בין 2°C ל 8°C).

אין להקפיא.

יש לאחסן באריזה המקורית כדי להגן מפני אור.

יש להוציא מהמקרר 30 דקות לפני השימוש.

~~אין להשתמש בתכשיר שהושאר בטמפרטורת החדר יותר מ- 12 שעות.~~

ניתן לאחסן את העט מזרק המוכן לשימוש בטמפרטורת החדר (עד 25°C) כשהוא מוגן מאור במשך 12 שעות לכל היותר. לאחר הוצאתו מהמקרר **יש להשתמש בו תוך 12 שעות או להשליכו.**

(...)

הוראות שלב אחר שלב להזרקה בעט המזרק המוכן לשימוש

(...)

בחר את אזור ההזרקה

(...)

- אם אתה זקוק לשתי זריקות להשלמת המינון, השאר לפחות 5 ס"מ בין כל מקום הזרקה אם אתה מזריק באותו אזור.

(...)

קיימים עדכונים נוספים. למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן המעודכנים.
העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#/byDrug
וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
ארינה שייקביץ
רוקחת ממונה