פברואר 2021

הנדון: <u>שינוי התוויה ועדכון עלונים עם הוספת התווית ילדים מעל גיל 5</u>

Benlysta 120 mg
בנליסטה 120 מ"ג
Benlysta 400 mg
בנליסטה 400 מ"ג

Powder for concentrate for solution for infusion

אבקה להכנת תמיסה מרוכזת להכנת תמיסה לעירוי

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשירים בנליסטה 120 מ"ג ו- בנליסטה 400 מ"ג.

בהודעה זו מצויינים העדכונים המהותיים בלבד.

מרכיבים פעילים וחוזקם:

BELIMUMAB 120 MG (80 mg/ml after reconstitution)
BELIMUMAB 400 MG (80 mg/ml after reconstitution)

התוויה הרשומה לתכשיר בישראל:

Benlysta is indicated as add-on therapy in patients aged 5 years and older 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.

שינוי בהתוויה – הוספת התווית ילדים מעל גיל 5:

Benlysta is indicated as add-on therapy in ~~adult~~ patients aged 5 years and older 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.

עדכונים מהותיים שנעשו בעלון לרופא:

4.1 Therapeutic indications

Benlysta is indicated as add-on therapy in ~~adult~~ patients aged 5 years and older 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).

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

4.2 Posology and method of administration

(…)

Paediatric population

The recommended dose regimen for children aged 5 years and older is 10 mg/kg Benlysta on Days 0, 14 and 28, and at 4-week intervals thereafter.

The safety and efficacy of Benlysta in children ~~and adolescents (<18 years~~ aged below 5 years ~~of age)~~ has not been established. No data are available.

(…)

4.4 Special warnings and precautions for use

(…)

Infections

The mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and younger children may be at increased risk.

(…)

4.8 Undesirable effects

(…)

Paediatric population

The adverse reaction profile in paediatric patients is based on 52-week safety data from a placebo-controlled study in which 53 patients (6 to 17 years of age) with SLE received Benlysta (10 mg/kg intravenously on Days 0, 14, 28, and then every 28 days, on a background of concomitant treatments). No new safety signals were observed in the paediatric population 12 years of age and above (n=43). Safety data in children younger than 12 years of age (n=10) are limited.

Infections

5- to 11-year-old group: infections were reported in 8/10 patients receiving Benlysta and 3/3 patients receiving placebo, and serious infections were reported in 1/10 patients receiving Benlysta and 2/3 patients receiving placebo (see section 4.4).

12- to 17-year-old group: infections were reported in 22/43 patients receiving Benlysta and 25/37 patients receiving placebo, and serious infections were reported in 3/43 patients receiving Benlysta and 3/37 patients receiving placebo. In the open-label extension phase there was one fatal infection in a patient receiving Benlysta.

(…)

5.1 Pharmacodynamic properties

Paediatric population

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Benlysta in one or more subsets of the paediatric population in SLE (see section 4.2 for information on paediatric use).~~

The safety and efficacy of Benlysta was evaluated in a randomised, double-blind, placebo-controlled, 52-week study (PLUTO) in 93 paediatric patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had active SLE disease, defined as a SELENA-SLEDAI score ≥6 and positive autoantibodies at screening as described in the adult trials. Patients were on a stable SLE treatment regimen (standard of care) and had similar inclusion criteria as the adult studies. Patients who had severe active lupus nephritis, severe active CNS lupus, primary immunodeficiency, IgA deficiency or acute or chronic infections requiring management were excluded from the study. The study was conducted in the US, South America, Europe, and Asia. Patient median age was 15 years (range 6 to 17 years). In the 5- to 11-year-old-group (n=13) the SELENA-SLEDAI score ranged from 4 to 13, and in 12- to 17-year-old-group (n=79) the SELENA-SLEDAI score ranged from 4 to 20. The majority (94.6%) of patients were female. The study was not powered for any statistical comparisons and all data are descriptive.

The primary efficacy endpoint was the SLE Responder Index (SRI) at Week 52 as described in the adult intravenous trials. There was a higher proportion of paediatric patients achieving an SRI response in patients receiving Benlysta compared with placebo. The response for the individual components of the endpoint were consistent with that of the SRI (Table 3).

Table 3 – Paediatric response rate at Week 52

Response	**Placebo (n=40)**	**Benlysta 10 mg/kg (n=53)**
SLE Responder Index (%)	43.6 (17/39)	52.8 (28/53)
Odds ratio (95% CI) vs placebo		1.49 (0.64, 3.46)
Components of SLE Responder Index		
Percent of patients with reduction in SELENA-SLEDAI ≥4 (%)	43.6 (17/39)	54.7 (29/53)
Odds ratio (95% CI) vs placebo		1.62 (0.69, 3.78)
Percent of patients with no worsening by BILAG index (%)	61.5 (24/39)	73.6 (39/53)
Odds ratio (95% CI) vs placebo		1.96 (0.77, 4.97)
Percent of patients with no worsening by PGA (%)	66.7 (26/39)	75.5 (40/53)
Odds ratio (95% CI) vs placebo		1.70 (0.66, 4.39)

Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0% of the Benlysta group compared to 35.0% of the placebo group over the 52 weeks of observation (observed treatment difference = 18.0%; hazard ratio = 0.36, 95% CI: 0.15, 0.86). This was consistent with the findings from the adult intravenous clinical trials.

Using the Paediatric Rheumatology International Trials Organisation/American College of Rheumatology (PRINTO/ACR) Juvenile SLE Response Evaluation Criteria, a higher proportion of paediatric patients receiving Benlysta demonstrated improvement compared with placebo (Table 4).

Table 4 – PRINTO/ACR response rate at Week 52

	Proportion of patients with at least 50% improvement in any 2 of 5 components* and no more than one of the remaining worsening by more than 30%		**Proportion of patients with at least 30% improvement in 3 of 5 components* and no more than one of the remaining worsening more than 30%**	
	Placebo n=40	**Benlysta 10 mg/kg n=53**	**Placebo n=40**	**Benlysta 10 mg/kg n=53**
Response, n (%)	14/40 (35.0)	32/53 (60.4)	11/40 (27.5)	28/53 (52.8)

Observed difference vs Placebo		25.38		25.33
Odds ratio (95% CI) vs Placebo		2.74 (1.15, 6.54)		2.92 (1.19, 7.17)

*The five PRINTO/ACR components were percent change at Week 52 in: Parent's Global Assessment (Parent GA), PGA, SELENA SLEDAI score, 24-hour proteinuria, and, Paediatric Quality of Life Inventory – Generic Core Scale (PedsQL GC) physical functioning domain score.

5.2 Pharmacokinetic properties

(…)

Special patient populations

Paediatric population: The pharmacokinetic parameters are based on individual parameter estimates from a population pharmacokinetic analysis of 53 patients from a study in paediatric patients. Following intravenous administration of 10 mg/kg on Days 0, 14 and 28, and at 4-week intervals thereafter, belimumab exposures were similar between paediatric and adult SLE subjects. Steady-state geometric mean Cmax, Cmin, and AUC values were 305 µg/mL, 42 µg/mL, and 2569 day•µg/mL in the 5- to 11-year-old-group, and 317 µg/mL, 52 µg/mL, and 3126 day•µg/mL in the 12- to 17-year-old-group (n=43). ~~No pharmacokinetic data are available in paediatric patients.~~

(…)

6.6 Special precautions for disposal and other handling

Preparation of 120 mg solution for infusion

Reconstitution

(…)

Dilution

The reconstituted medicinal product is diluted to 250 ml with sodium chloride 9 mg/ml (0.9%), sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 ml of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/ml.

(…)

עדכונים מהותיים שנעשו בעלון לצרכן:

1. למה מיועדת התרופה?

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

בנליסטה מיועדת כתוספת טיפול במטופלים מגיל 5 שנים ומעלה 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.

2. לפני שימוש בתרופה

(…)

ילדים

תרופה זו אינה מיועדת לשימוש בילדים מתחת לגיל 5 שנים.

(…)

4. תופעות לוואי

(…)

זיהומים

בנליסטה עלולה לגרום לך להדבק בזיהומים בסבירות גבוהה יותר, כולל זיהומים בדרכי השתן והנשימה, ילדים צעירים יותר עלולים להיות בסיכון מוגבר.

(…)

Instructions for use and handling – reconstitution, dilution and administration

(…)

3) How to dilute the solution for infusion

The reconstituted medicinal product is diluted to 250 ml with sodium chloride 9 mg/ml (0.9%), sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 ml of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/ml.

(…)

מקרא לעדכונים המסומנים:

תוספת – כתב **כחול**; תוספת החמרה – כתב **כחול** – מסומן בצהוב מרקר; מידע שהוסר – מסומן בקו אדום חוצה ~~XXX~~

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