תאריך : נובמבר 2018

הנדון: **נוקלה / Nucala**
Mepolizumab 100 mg
Powder for solution for injection
S.C

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,
חברת גלקסוסמיתקליין ישראל בע"מ (GSK) שמחה להודיע על רישומה של התוויה נוספת עבור נוקלה, ועדכון העלונים לרופא ולצרכן בהתאם.

ההתוויה כפי שהייתה רשומה עד היום לתכשיר בישראל:

Severe Asthma
As an add-on treatment for severe refractory eosinophilic asthma in adult patients

ההתוויה החדשה שהתווספה (מסומנת בצהוב):

Severe Asthma
As an add-on treatment for severe refractory eosinophilic asthma in adult patients
Eosinophilic Granulomatosis with Polyangiitis:
For the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

משטר המינון להתוויה החדשה שהתווספה:

The recommended dosage of Nucala is 300 mg administered once every 4 weeks by SC injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen

בעקבות תוספת ההתוויה נעשו השינויים הבאים בעלונים:

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא:

4.2 Posology and method of administration

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma **or EGPA**.

Posology

Adults

Severe Asthma

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. Nucala is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.

Eosinophilic Granulomatosis with Polyangiitis

The recommended dosage of Nucala is 300 mg administered once every 4 weeks by SC injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen. It is recommended that the individual 100-mg injections be administered at least 5 cm (approximately 2 inches) apart if more than 1 injection is administered at the same site.

Preparation of the 300-mg dose for treatment of EGPA requires the reconstitution of 3 separate 100-mg vials as described below (see Method of Administration).

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/µL at week 32 (N=182), a reduction of 84% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment.

Following SC administration of mepolizumab 300 mg every 4 weeks for 52 weeks in subjects with EGPA, blood eosinophils were reduced to a geometric mean count of 38 cells/mcL. There was a geometric mean reduction of 83% compared with placebo and this magnitude of reduction was observed within 4 weeks of treatment [see Clinical efficacy].

Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of subjects treated with 100 mg dose subcutaneously developed anti-mepolizumab antibodies after having received at least one dose of mepolizumab. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

In subjects with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any subjects with EGPA.
The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Clinical efficacy
Severe Asthma
.....
Eosinophilic Granulomatosis with Polyangiitis
A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT #02020889). Subjects received 300 mg of NUCALA or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. The co-primary endpoints were the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of subjects in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.
The demographics and baseline characteristics of subjects in this trial are provided in Table 5.

Table 5. Demographics and Baseline Characteristics in EGPA

	N = 136
Mean age (y)	48.5
Female, n (%)	80 (59)
White, n (%)	125 (92)
Duration (y) of EGPA, mean (SD)	5.5 (4.63)
History of ≥1 confirmed relapse in past 2 years, n (%)	100 (74)
Refractory disease, n (%) Recurrence of EGPA symptoms, n (%) Failed induction treatment, n (%)	74 (54) 68 (50) 6 (4)
Baseline oral corticosteroid[a] daily dose (mg), median (range)	12 (7.5-50)
Receiving immunosuppressive therapy[b], n (%)	72 (53)

[a] Prednisone or prednisolone equivalent.
[b] e.g., Azathioprine, methotrexate, mycophenolic acid.
EGPA = eosinophilic granulomatosis with polyangiitis, SD = standard deviation.

Remission
Subjects receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of subjects receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (Table 6). Results of the components of remission are also shown in Table 6. In addition, significantly more subjects receiving 300 mg of NUCALA achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for 300 mg of NUCALA versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

Table 6. Remission and Components of Remission in EGPA

	Remission (OCS ≤4 mg/day + BVAS = 0)		OCS ≤4 mg/day		BVAS = 0	
	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68
Accrued duration over 52 weeks, n (%)						
0	55 (81)	32 (47)	46 (68)	27 (40)	6 (9)	3 (4)
>0 to <12 weeks	8 (12)	8 (12)	12 (18)	5 (7)	15 (22)	13 (19)
12 to <24 weeks	3 (4)	9 (13)	6 (9)	12 (18)	11 (16)	5 (7)
24 to <36 weeks	0	10 (15)	2 (3)	10 (15)	17 (25)	2 (3)
≥36 weeks	2 (3)	9 (13)	2 (3)	14 (21)	19 (28)	45 (66)
Odds ratio (mepolizumab/placebo)[a] (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of subjects at both Weeks 36 and 48						
Subjects, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (mepolizumab/placebo)[a] (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

[a] An odds ratio >1 favors mepolizumab.

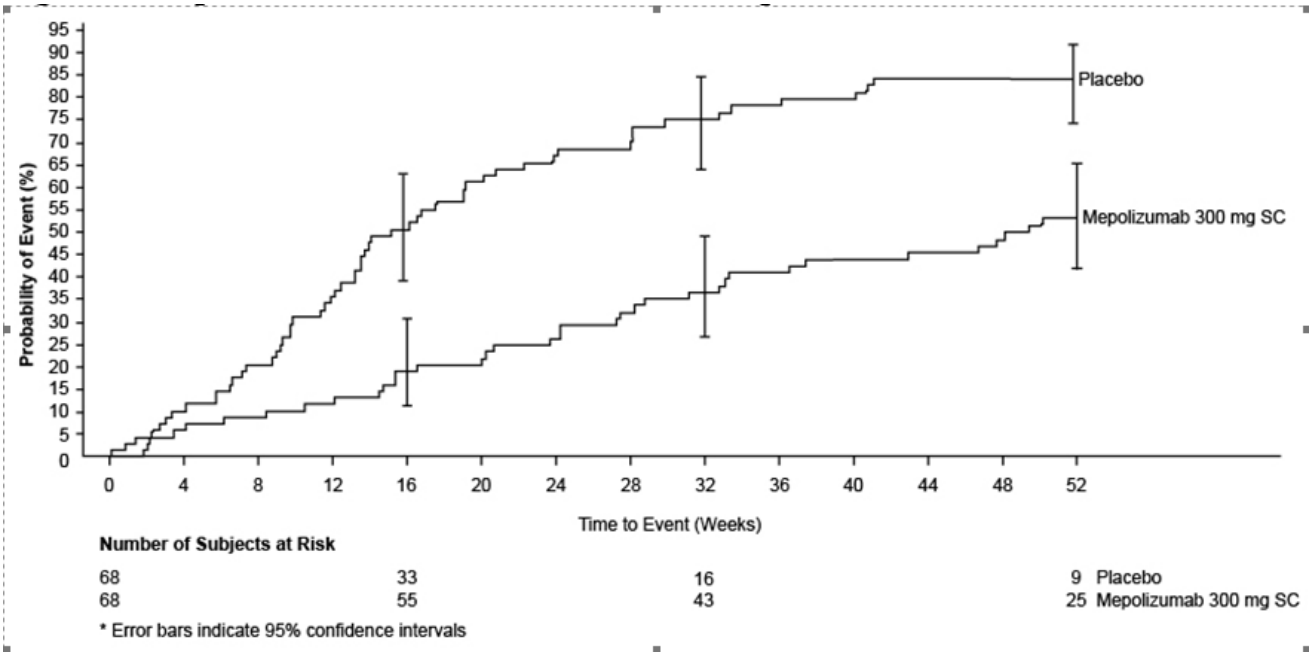
EGPA = eosinophilic granulomatosis with polyangiitis, OCS = oral corticosteroid, BVAS = Birmingham Vasculitis Activity Score.

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day.

Relapse

The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for subjects receiving 300 mg of NUCALA compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 2). Additionally, subjects receiving 300 mg of NUCALA had a reduction in rate of relapse compared with subjects receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for 300 mg of NUCALA compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with mepolizumab compared with placebo.

Figure 2. Kaplan-Meier Plot of Time to First Relapse in EGPA



Corticosteroid Reduction

Subjects receiving 300 mg of NUCALA had a significantly greater reduction in average daily OCS dose compared with subjects receiving placebo during Weeks 48 to 52 (Table 7).

Table 7. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of Subjects	
	Placebo n = 68	NUCALA 300 mg n = 68
0	2 (3)	12 (18)
>0 to ⩽4.0 mg	3 (4)	18 (26)
>4.0 to ⩽7.5 mg	18 (26)	10 (15)
>7.5 mg	45 (66)	28 (41)
Comparison: mepolizumab/placebo[a]		
Odds ratio[b]		0.20
95% CI		0.09, 0.41

[a] Analyzed using a proportional odds model with covariates of treatment group, baseline oral corticosteroid daily dose, baseline Birmingham Vasculitis Activity Score, and region.

[b] An odds ratio <1 favors mepolizumab.

Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the subject, was developed to measure the adequacy of asthma control and change in asthma control. The on-treatment ACQ-6 responder rate during Weeks 48 to 52 (defined as a decrease in score of 0.5 or more compared with baseline) was 22% for 300 mg of NUCALA and 16% for placebo (OR 1.56; 95% CI: 0.63, 3.88 for 300 mg of NUCALA compared with placebo).

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg.

The pharmacokinetic properties of mepolizumab observed in subjects with EGPA were similar to the pharmacokinetic properties observed in subjects with severe asthma.

Systemic exposure following administration of mepolizumab 300 mg subcutaneously in subjects with EGPA was approximately 3 times that of mepolizumab 100 mg administered subcutaneously in subjects with severe asthma (Trial 2).

<u>עדכונים מהותיים נעשו בסעיפים הבאים בעלון לצרכן :</u>

1. <u>למה מיועדת התרופה?</u>

התרופה משמשת לטיפול:

- בחולים מבוגרים עם **אסטמה אאוזינופילית חמורה** שאינה מגיבה לטיפולים אחרים בשילוב עם תרופות נוספות.
- **בחולים מבוגרים עם דלקת כלי דם אלרגית וגרנולומטוטית - מחלת צ'ורג-שטראוס Eosinophilic Granulomatosis with Polyangiitis (EGPA)**

3. <u>כיצד תשתמש בתרופה?</u>

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.

נוקלה ניתנת על-ידי רופא, אחות או איש מקצוע רפואי אחר בהזרקה מתחת לעור (subcutaneously).

המינון המקובל בדרך כלל הוא:

לטיפול באסטמה אאוזינופילית חמורה - 100 מ"ג, זריקה אחת כל 4 שבועות.

דלקת כלי דם אלרגית וגרנולומטוטית - 300 מ"ג, (3 זריקות של 100 מ"ג), בפעם אחת כל 4 שבועות

בהודעה זו מצויינים העדכונים המהותיים בלבד.

קיימים עדכונים נוספים. למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן המעודכנים.

<u>מקרא לעדכונים המסומנים:</u>

תוספת החמרה - כתב **כחול** - מסומן בצהוב מרקר

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
שרית רוזן
רוקחת ממונה