ינואר 2026

<u>הנדון:</u>

נוקלה תמיסה להזרקה
<u>Nucala Solution for Injection</u>
<u>מרכיב פעיל וחוזקו: mepolizumab 100mg / 1mL</u>

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על:

1. **אישורה של התוויה נוספת** לתכשיר שבנדון.

להלן ההתוויות הרשומות לתכשיר, ההתוויה הנוספת שאושרה מסומנת בכחול:

<u>Severe eosinophilic asthma</u>
Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients.

<u>Chronic rhinosinusitis with nasal polyps (CRSwNP)</u>
Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with corticosteroids and surgery in the last 10 years do not provide adequate disease control.

<u>Eosinophilic Granulomatosis with Polyangiitis (EGPA)</u>
Nucala is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

<u>Hypereosinophilic syndrome (HES)</u>
Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.

<u>Chronic obstructive pulmonary disease (COPD)</u>
Nucala is indicated as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease with an eosinophilic phenotype.

2. **עדכון העלונים** לרופא ולצרכן של התכשיר.

בהודעה זו מצויינים העדכונים המהותיים בלבד. העלונים כוללים עדכונים נוספים. תוספת מידע

מסומנת באדום, מחיקת מידע מסומנת בקו חוצה-כחול. תוספת החמרה מסומנת ברקע צהוב.

העדכונים המהותיים בעלון לרופא:

4.1 Therapeutic indications

(…)

Chronic obstructive pulmonary disease (COPD)
Nucala is indicated as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease with an eosinophilic phenotype.

(…)

4.2 Posology and method of administration

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, CRSwNP, COPD, EGPA or HES.
(…)

Posology
(…)

COPD
Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Limitations:
For the indication of COPD, mepolizumab may be used in patients with an eosinophil level above 150 cells/µL.

(…)

4.4 Special warnings and precautions for use

(…)

Asthma or COPD exacerbations
Mepolizumab should not be used to treat acute asthma or COPD exacerbations.

Asthma-related or COPD-related adverse symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma or COPD remains uncontrolled or worsens after initiation of treatment.

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4.8 Undesirable effects

(…)

COPD
Adverse Reactions in Adults with Chronic Obstructive Pulmonary Disease

The safety data below reflects the safety of NUCALA in adults with inadequately controlled COPD and an eosinophilic phenotype. NUCALA was evaluated in a pooled safety population that consisted of 2089 patients with COPD in 3 randomized, placebo-controlled, multicenter trials of 52 to 104 weeks duration, including MATINEE and METREX , and Trial 3. Trial 3 enrolled COPD adults

with a peripheral blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the year prior. The pooled safety population received NUCALA 100 mg (n = 1043) or placebo (n = 1046), administered subcutaneously once every 4 weeks, in addition to background triple inhaled therapies (e.g., ICS, long-acting beta agonist [LABA], and long-acting muscarinic antagonist [LAMA]).

The table below summarizes adverse reactions that occurred in ≥3% of patients treated with NUCALA and more frequently than in patients treated with placebo in COPD trials.

Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with Chronic Obstructive Pulmonary Disease in a Pooled Safety Population (MATINEE, METREX, and Trial 3)

Adverse Reaction	**NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 1043) %**	**Placebo (n = 1046) %**
Back pain	7	6
Diarrhea	5	4
Cough	5	4
Oropharyngeal pain	4	2
Urinary tract infection	4	3
Pain in extremity	4	3

Herpes Zoster: In the pooled safety population, 14 (1%) patients in the NUCALA group compared to 7 (0.7%) patients in the placebo group experienced herpes zoster.

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX09.

Mechanism of action

Mepolizumab is an IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, COPD, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma, CRSwNP, COPD, EGPA, and HES has not been definitively established.

Pharmacodynamic effects

(…)

COPD

Following subcutaneous administration of NUCALA 100 mg every 4 weeks blood eosinophils were reduced to a similar magnitude to that observed in patients with severe asthma compared to placebo.

For adults with COPD, following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 52 to 104 weeks, blood eosinophils were reduced to a geometric mean count of 50-60 cells/mcL. There was a geometric mean reduction of approximately 79% compared with placebo, and this magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, COPD, EGPA and HES

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 with severe refractory eosinophilic asthma treated with 100 mg dose, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of subjects with HES treated with 300 mg dose of mepolizumab subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.

The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) or in HES patients (n=102) treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies.

In patients receiving NUCALA 100 mg over 52 to 104 weeks for COPD, 36/996 (4%) had detectable anti-mepolizumab antibodies.

Neutralising antibodies were detected in one adult patient with severe refractory eosinophilic asthma and in no patients with CRSwNP COPD, EGPA or HES. 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.

(…)

Chronic Obstructive Pulmonary Disease (COPD)

The efficacy of NUCALA as add-on maintenance treatment for adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials (MATINEE [NCT04133909] and METREX [NCT02105948]). The two trials enrolled a total of 1640 adults who were randomized to receive NUCALA 100 mg or placebo administered subcutaneously every 4 weeks for a treatment duration of 52 to 104 weeks in MATINEE or 52 weeks in METREX. While 1640 adults were enrolled in the two clinical trials (MATINEE and METREX), the efficacy population consisted of 1266 adults.

Both trials enrolled patients with a diagnosis of COPD with moderate to very severe airflow limitation (post-bronchodilator FEV_1/FVC ratio <0.7 and post-bronchodilator FEV_1 of 20% to 80% predicted) and at least 2 moderate or 1 severe COPD exacerbation in the previous year despite receiving triple inhaled therapy.

In MATINEE, patients were required to have a minimum blood eosinophil count of 300 cell/mcL at screening. In METREX, there was no minimum blood eosinophil count requirement, but

randomization was stratified by baseline blood eosinophil count: ≥150 cell/mcL at screening or ≥300 cell/mcL in the previous 12 months, or blood eosinophil count <150 cells/mcL at screening with no evidence of blood eosinophil count ≥300 cell/mcL in the previous 12 months. There was insufficient data from METREX to support the efficacy of NUCALA in patients with COPD with blood eosinophil count <150 cells/mcL at screening with no evidence of blood eosinophil count ≥300 cell/mcL in the previous 12 months. Thus, the efficacy population (N = 1266) included patients from MATINEE (n = 804) and patients from METREX who had a blood eosinophil count ≥150 cell/mcL at screening or ≥300 cell/mcL in the previous 12 months (n = 462). The data from this efficacy population is described below.

The demographic and baseline characteristics of MATINEE and METREX efficacy population are provided in the table below.

Demographics and Baseline Characteristics of Patients with Chronic Obstructive Pulmonary Disease in MATINEE and METREX[a] Trials

	MATINEE	**METREX[a]**
	N = 804	**N = 462**
Mean age (y) (SD)	66 (8.0)	65 (8.4)
Female, n (%)	253 (31)	163 (35)
White, n (%)	673 (84)	391 (85)
Asian, n (%)	112 (14)	5 (1)
Black or African American, n (%)	10 (1)	6 (1)
Other/Multiple, n (%)	9 (1)	60 (13)
Hispanic/Latino, n (%)	189 (24)	75 (16)
Current smokers, n (%)	222 (28)	134 (29)
Average smoking history (pack-years) (SD)	43 (24.9)	44 (25.8)
Post-bronchodilator % predicted FEV_1, mean (SD)	48 (15.8)	44 (14.8)
Post-bronchodilator FEV_1/FVC, mean (SD)	0.5 (0.12)	0.5 (0.12)
Mean number of moderate[b] or severe[c] exacerbations in previous year (SD)	2.3 (0.94)	2.5 (1.29)
Background COPD medications at randomization: ICS/LAMA/LABA, n (%)	794 (99)	454 (98)
SGRQ score, mean (SD)	55 (17.8)	55 (16.7)
Geometric mean eosinophil count at screening, cells/mcL (95% CI)	480 (470, 490)	260 (250, 280)

SD = standard deviation, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroids, LAMA = long-acting muscarinic antagonist, LABA = long-acting beta agonist, SGRQ = St. George's Respiratory Questionnaire, CI = confidence interval.

[a] Patients with blood eosinophil count ≥150 cell/mcL at screening or ≥300 cell/mcL in the previous 12 months only.

[b] Exacerbations treated with either systemic corticosteroids with or without antibiotics.

[c] Exacerbations requiring hospitalization.

Annualized Rate of Moderate or Severe Exacerbations in Adult Patients with Chronic Obstructive Pulmonary Disease

The primary endpoint for the MATINEE and METREX trials was the annualized rate of moderate or severe exacerbations during the 52 to 104-week and 52-week treatment periods, respectively. Moderate exacerbations are defined per protocol as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hours) or result in death.

In both trials, NUCALA demonstrated a statistically significant reduction in the annualized rate of moderate or severe exacerbations compared with placebo when added to triple inhaled therapy (see Table below).

Annualized Rate of Moderate[a] or Severe[b] Exacerbations in MATINEE and METREX Trials

	MATINEE		**METREX[c]**	
	NUCALA N = 403	**Placebo N = 401**	**NUCALA N = 233**	**Placebo N = 229**
Exacerbation rate per year	0.80	1.01	1.40	1.71
Rate ratio vs. placebo (95% CI)	0.79 (0.66, 0.94)		0.82 (0.68, 0.98)	

CI = confidence interval.
[a] Exacerbations treated with either systemic corticosteroids/antibiotics.
[b] Exacerbations requiring hospitalization or resulting in death.
[c] Patients with baseline eosinophils ≥150 cell/mcL at screening or ≥300 cell/mcL in the previous 12 months.

The time to first event analysis showed a statistically significant reduction in the risk of moderate or severe exacerbation for patients receiving NUCALA compared to placebo (HR: 0.77; 95% CI: 0.64, 0.93) through 104 weeks in MATINEE.

NUCALA reduced the annualized rate of COPD exacerbations requiring emergency department visits and/or hospitalization when compared with placebo (rate ratio [RR] of 0.65; 95% CI: 0.43, 0.96 [not statistically significant due to failure of an endpoint higher in the pre-defined testing hierarchy]) in MATINEE.

Health Related Quality of Life
In MATINEE and METREX, the St. George's Respiratory Questionnaire (SGRQ) total score responder rate (defined as the proportion of subjects with SGRQ improvement from baseline of at least 4 points) at Week 52 was evaluated. In MATINEE, the responder rate was 50% in the NUCALA group compared with 46% in the placebo group (N = 783, odds ratio [OR]: 1.17; 95% CI: 0.87, 1.57). In the METREX efficacy population, the responder rate was 42% in the NUCALA group compared to 40% in the placebo group (N = 451, odds ratio [OR]: 1.08; 95% CI: 0.74, 1.59).

<u>העדכונים המהותיים בעלון לצרכן:</u>

1. למה מיועדת התרופה?

(...)

בחולים מבוגרים עם **מחלת ריאות חסימתית כרונית** (Chronic Obstructive Pulmonary Disease, COPD) שאינה נשלטת כראוי, עם פנוטיפ אאוזינופילי. התרופה ניתנת כטיפול תחזוקתי בשילוב עם תרופות נוספות.

(...)

קבוצה תרפויטית

(...)

- **מחלת ריאות חסימתית כרונית (COPD)** לחלק מהאנשים עם מחלת ריאות חסימתית כרונית יש יותר מדי *אאוזינופילים* (סוג של תא דם לבן) בדם ובריאות, דבר שגורם לדרכי הנשימה להיות דלקתיות ומעובות. מצב זה מתמשך לאורך זמן ולאט לאט מחמיר. התסמינים כוללים קוצר נשימה, שיעול, אי-נוחות בחזה ושיעול ריריי. נוקלה תמיסה להזרקה מפחיתה את מספר האאוזינופילים בדם ויכולה להפחית התלקחויות של תסמיני COPD .

(...)

2. לפני השימוש בתרופה

(...)

<u>החרפה באסטמה או ב COPD</u>

ישנם אנשים אשר חווים תופעות לוואי הקשורות למחלת האסטמה או למחלת ה COPD שלהם, או שמחלות אלה שלהם עלולות להחמיר במהלך הטיפול בנוקלה תמיסה להזרקה.

← **ספר לרופא או לאחות** אם מחלת האסטמה או מחלת ה COPD שלך אינה נשלטת, או מחמירה, לאחר תחילת הטיפול בנוקלה תמיסה להזרקה.

(...)

אינטראקציות/תגובות בין תרופתיות

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

תרופות אחרות לטיפול באסטמה, בדלקת כרונית חמורה במערות האף המלווה בפוליפים אפיים, במחלת ריאות חסימתית כרונית, בדלקת כלי דם אלרגית וגרנולומטוטית או בתסמונת היפר-אאוזינופילית.

אל תפסיק באופן פתאומי נטילת תרופות אחרות שלך לטיפול באסטמה, בדלקת כרונית חמורה במערות

האף המלווה בפוליפים אפיים, במחלת ריאות חסימתית כרונית, (...)

3.כיצד תשתמש בתרופה

המינון המקובל בדרך כלל הוא:

(...)

- **לטיפול במחלת ריאות חסימתית כרונית (COPD) -** 100 מ"ג, זריקה תת-עורית אחת בכל 4 שבועות.

(...)

4. תופעות לוואי

(...)

תופעות לוואי שכיחות

(...)

- שלשול
- שיעול

(...)

למידע נוסף יש לעיין בעלונים המעודכנים.
העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
מאגר התרופות (health.gov.il) וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח-תקוה בטלפון: 03-9297100

בברכה,
ענבל גבע דותן
רוקחת ממונה