[GSK logo]

NUCALA

Mepolizumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

A clear to opalescent, colourless to pale yellow to pale brown solution in a single-use, pre-filled pen or syringe.

Each pre-filled pen (auto-injector) or pre-filled syringe (safety-syringe) delivers 100 mg mepolizumab in 1 mL (100 mg/mL).

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), directed against human interleukin-5 (IL-5) produced in Chinese hamster ovary cells by recombinant DNA technology.

PHARMACEUTICAL FORM:

Solution for injection in a 100mg/ml pre-filled pen (auto-injector)

Solution for injection in a 100mg/ml pre-filled syringe (safety syringe)

CLINICAL PARTICULARS

Indications

Severe Eosinophilic Asthma

NUCALA is indicated as an add-on maintenance treatment for patients aged 12 years old and older with severe eosinophilic asthma who:

- have at least two exacerbations in the preceding 12 months on current standard of care (high doses of inhaled corticosteroids plus additional maintenance treatment) and/or requirement for treatment with systemic corticosteroids, and
- have a blood eosinophil count of ≥ 150 cells/µL (0.15 GI/L) at initiation of treatment with *NUCALA* OR ≥ 300 cells/µL (0.3 GI/L) in the past 12 months.

NUCALA is not indicated for other eosinophilic conditions or for relief of acute bronchospasm or status asthmaticus (*see Warnings and Precautions).*

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

NUCALA is indicated as add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over.

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Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Dosage and Administration

NUCALA should be prescribed by a specialist experienced in the diagnosis and treatment of severe eosinophilic asthma.

NUCALA should only be administered as a subcutaneous injection (see *Special precautions for disposal and other handling* and *Instructions for Use*).

NUCALA may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate and the patient or caregiver are trained in injection techniques.

Posology

Severe Eosinophilic asthma

Adults and Adolescents (12 years and older)

The recommended dose is 100 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

The safety and efficacy of *NUCALA* have not been established in adolescents weighing less than 45kg.

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.

Children (up to 12 years of age)

The safety and efficacy of *NUCALA* have not been established in children less than 12 years of age.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Injection sites should be at least 5 cm apart (see *Special precautions for disposal and other handling and Instructions for Use).*

Adults

The recommended dose is 300 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children and adolescents under 18 years of age

The safety and efficacy of Nucala has not been tested in adolescents and children with

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EGPA who are under 18 years of age.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Adults

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

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

Children

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

Elderly (65 years or older)

No dosage adjustment is recommended in patients 65 years or older (see *Pharmacokinetics – Special Patient Populations*).

Renal Impairment

Dose adjustments in patients with renal impairment are unlikely to be required *(*see *Pharmacokinetics – Special Patient Populations).*

Hepatic Impairment

Dose adjustments in patients with hepatic impairment are unlikely to be required *(*see *Pharmacokinetics – Special Patient Populations).*

Contraindications

Hypersensitivity to mepolizumab or to any of the excipients.

Warnings and Precautions

NUCALA should not be used to treat acute asthma exacerbations. ~~or COPD exacerbations.~~

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

Abrupt discontinuation of corticosteroids after initiation of *NUCALA* therapy is not recommended. Reductions in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

Hypersensitivity and Administration Reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis,

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urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of *NUCALA*. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days).

Parasitic Infections

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Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical programme. Patients with pre-existing helminth infections should be treated for their infection prior to *NUCALA* therapy. If patients become infected whilst receiving treatment with *NUCALA* and do not respond to anti-helminth treatment, temporary discontinuation of *NUCALA* should be considered.

Interactions

No formal interaction studies have been performed with *NUCALA*.

Pregnancy and Lactation

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti- IL5 treatment on fertility (see *Non-Clinical Information*).

Pregnancy

The effect of *NUCALA* on human pregnancy is unknown. No treatment related effects on embryo-foetal or postnatal development have been shown in animal studies (see *Non- Clinical Information*).

NUCALA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Lactation

There are no data regarding the excretion of *NUCALA* in human milk. However, mepolizumab was excreted into the milk of cynomolgous monkeys at concentrations that were less than 0.5% of those detected in plasma.

A decision should be made whether to discontinue breast-feeding or discontinue *NUCALA*, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *NUCALA* on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology or adverse reaction profile of *NUCALA*.

Adverse Reactions

Clinical trial experiences

Severe Eosinophilic Asthma

The safety of *NUCALA* was studied in a clinical development program in adolescents and adults with severe eosinophilic asthma which included 3 randomised, placebo-controlled, multicentre studies (n=1327). Subjects received either subcutaneous (SC) or intravenous (IV) mepolizumab or placebo during clinical studies of 24-52 weeks duration. Adverse reactions associated with *NUCALA* 100 mg administered subcutaneously (n=263) are presented in the table below. The safety profile of *NUCALA* in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

System Organ Class	Adverse Reactions	Frequency
Infections & Infestations	Pharyngitis Lower respiratory tract infection Urinary tract infection	Common Common Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous System Disorders	Headache	Very common
Respiratory, Thoracic & Mediastinal Disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back Pain	Common
General disorders and administration site conditions	Pyrexia Injection site reactions*** Administration-related reactions (systemic non allergic)***	Common Common

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies. For examples of the associated manifestations reported and a description of the time to onset, see Warnings and Precautions.

**From spontaneous post marketing reporting.

*** The most common symptoms associated with subcutaneous injections included: pain, erythema,

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swelling, itching, and burning sensation.

**** The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

In a double-blind placebo-controlled study in subjects with EGPA (300 mg *NUCALA* n=68, placebo n=68) no additional adverse reactions were identified to those reported for the severe asthma studies.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

In a randomised, double-blind placebo-controlled 52-week study in subjects with CRSwNP (*NUCALA* 100 mg n= 206, placebo n= 201), no additional adverse reactions were identified to those reported for the severe asthma studies.

~~**Post-marketing data**~~

~~System Organ Class~~	~~Adverse reaction(s)~~	~~Frequency~~
~~Immune system disorders~~	~~Hypersensitivity reactions including anaphylaxis~~	~~Rare~~

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Overdose

There is no clinical experience with overdose of *NUCALA*.

Single doses of up to 1500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

Treatment

There is no specific treatment for an overdose with *NUCALA*. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases

R03DX09

Mechanism of action

NUCALA is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. *NUCALA* inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

Severe eosinophilic asthma

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with *NUCALA*. The magnitude and duration of this reduction was dose- dependent. Following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, the blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment. This magnitude of blood eosinophils reduction was maintained in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

In patients with EGPA, following a dose of 300 mg administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 38 cells/µL. There was a geometric mean reduction of 83% compared to placebo.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

In patients with CRSwNP, following a dose of 100 mg administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 60 cells/µL, which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

Immunogenicity

Severe eosinophilic asthma

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment.

In subjects who received at least one dose of mepolizumab administered subcutaneously every four weeks, 15/260 (6%) (100 mg, severe asthma) and 1/68 (1%) (300 mg, EGPA) had detectable anti-mepolizumab antibodies. The immunogenicity profile of mepolizumab in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

Neutralizing antibodies were detected in one subject receiving mepolizumab. Anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab treatment in the majority of patients and there was no evidence of a correlation between antibody tires and change in eosinophil level.

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Clinical Studies

Severe eosinophilic asthma

The efficacy of *NUCALA* in the treatment of a targeted group of subjects with severe eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These studies were designed to evaluate the efficacy of *NUCALA* administered once every 4 weeks by subcutaneous or intravenous injection in severe eosinophilic asthma patients not controlled on their standard of care [e.g., inhaled corticosteroids (ICS), oral corticosteroids (OCS), combination ICS and long-acting beta$_2$-adrenergic agonists (LABA), leukotriene modifiers, short-acting beta$_2$-adrenergic agonists (SABA)].

Placebo-Controlled Studies

Dose-ranging Efficacy MEA112997 (DREAM) Study

In MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 616 patients, results demonstrated that *NUCALA* (75 mg, 250 mg or 750 mg) significantly reduced asthma exacerbations when administered intravenously compared to placebo. There was no statistically significant difference in effect seen between the 3 studied doses. Blood eosinophil counts greater than or equal to 150 cells/µl at screening; or blood eosinophils ≥300 cells/µl in the past 12 months predicted subjects who would benefit most from *NUCALA* therapy. Results from this study were used to determine dose selection for the studies using subcutaneous *NUCALA* administration. *NUCALA* is not indicated for intravenous use, and should only be administered by the subcutaneous route.

Exacerbation Reduction MEA115588 (MENSA) Study

MEA115588 was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre-study which evaluated the efficacy and safety of *NUCALA* as add-on therapy in 576 patients with severe eosinophilic asthma. This study evaluated the frequency of clinically significant exacerbations of asthma, defined as: worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits.
Patients were aged 12 years of age or older, with a history of two or more asthma exacerbations in the past 12 months and not controlled on their current asthma drug therapies [i.e., high-dose inhaled corticosteroids (ICS) in combination with at least another controller such as long-acting beta$_2$-adrenergic agonists (LABA) or leukotriene modifiers]. Patients were allowed to be on oral corticosteroid therapy and continued to receive their existing asthma medication during the study. Severe eosinophilic asthma was defined as peripheral blood eosinophils greater than or equal to 150 cells/µl within 6 weeks of randomisation (first dose) or blood eosinophils greater than or equal to 300 cells/µl within the past 12 months of randomisation.
Patients received either *NUCALA* 100 mg administered subcutaneously (SC), *NUCALA* 75 mg administered intravenously (IV), or placebo treatment once every 4 weeks over 32-weeks.

The primary endpoint, reduction in the frequency of clinically significant exacerbations of asthma was statistically significant ($p<0.001$). Table 1, provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 1: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

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	NUCALA (100 mg SC) N=194	Placebo N=191
Primary endpoint		
Frequency of Clinically Significant Exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	–
p-value	<0.001	
Secondary endpoints		
Frequency of Exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of Exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	
Pre-bronchodilator FEV_1 (mL) at Week 32		
Mean Change from Baseline (SE)	183 (31.1)	86 (31.4)
Difference (mepolizumab vs. placebo)	98	
95% CI	11, 184	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Mean Change from Baseline (SE)	-16.0 (1.13)	-9.0 (1.16)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	-10.2, -3.8	
p-value	<0.001	

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Oral Corticosteroid Reduction MEA115575 (SIRIUS) Study

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MEA115575 evaluated the effect of *NUCALA* 100 mg SC on reducing the use of maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe eosinophilic asthma who were dependent on systemic corticosteroids.

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Patients had a peripheral blood eosinophil count of ≥300/μL in the 12 months prior screening or a peripheral blood eosinophil count of ≥150/μL at baseline. Patients were administered *NUCALA* or placebo treatment once every 4 weeks over the treatment period. The OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained. During the study patients continued their baseline asthma therapy [i.e., high-dose inhaled corticosteroids (ICS) in combination with at least another controller such as long-acting $beta_2$-adrenergic agonists (LABA) or leukotriene modifiers].

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This study enrolled a total of 135 patients: mean age of 50 years, 55% were female, 48% had been receiving oral steroid therapy for at least 5 years, and had a baseline mean prednisone equivalent dose of approximately 13 mg per day.

The primary endpoint was the reduction in daily OCS dose (weeks 20-24) whilst maintaining asthma control compared with patients treated with placebo (see Table 2).

Table 2: Results of the primary and secondary endpoints in the Intent to Treat population (MEA115575).

	NUCALA (100 mg SC) N=69	Placebo N=66
Primary Endpoint		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
90% - 100% 75% - <90% 50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	16 (23%) 12 (17%) 9 (13%) 7 (10%) 25 (36%)	7(11%) 5 (8%) 10 (15%) 7(11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
Secondary Endpoints		
Reduction in the daily OCS dose (%)		
At least 50% reduction	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	
p-value	0.027	
Reduction in the daily OCS dose (%)		
To ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Reduction in the daily OCS dose		
To 0 mg/Day	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0.414	
Median Percentage Reduction in Daily OCS Dose		
Median % reduction from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for *NUCALA* compared with placebo: -5.8 (95% CI: -10.6,-1.0; P=0.019). At Week 24, the proportion of subjects with a

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clinically meaningful decrease in SGRQ score (defined as a decrease of at least 4 units from baseline) was greater for *NUCALA* (58%, 40/69) compared with placebo (41%, 27/66).

The long-term efficacy profile of *NUCALA* in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies MEA115666, MEA115661 and 201312 was generally consistent with the 3 placebo- controlled studies.

Open Label Extension Study MEA115661 (COSMOS) Study

Following completion of the double-blind MEA115575 and MEA115588 studies, all patients were offered the opportunity to participate in MEA115661, a 52-week open-label extension (OLE) study, during which time all patients received open-label mepolizumab (100 mg SC). In total, 651 patients (126 subjects who had previously participated in study MEA115575 and 525 subjects who had previously participated in Study MEA115588), received 100 mg SC of mepolizumab every 4 weeks. During open-label treatment of all subjects with mepolizumab in MEA115661, the rates of exacerbations per year remained low in the subjects who were previously treated with mepolizumab and were consistent with results demonstrated during the 32-week double-blind period of study MEA115588. In addition, the impact of mepolizumab on steroid reduction was maintained following MEA115575 with average daily steroid dose remaining consistent with the level achieved with mepolizumab treatment at Weeks 20-24 during MEA115575.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52 week study which evaluated 136 patients ≥18 years old with relapsing or refractory EGPA and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone). Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients received a 300 mg dose of *NUCALA* or placebo administered subcutaneously once every 4 weeks in addition to their background prednisolone/prednisone with or without immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator.

The co-primary endpoints were the total accrued duration of remission, defined as a Birmingham Vasculitis Activity Score (BVAS)=0 (no active vasculitis) plus prednisolone/prednisone dose ≤4 mg/day, and the proportion of subjects in remission at both 36 and 48 weeks of treatment.

Remission

Compared with placebo, subjects receiving NUCALA 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of subjects receiving NUCALA 300 mg achieved remission at bothWeek 36 and Week 48 (Table 3).

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Table 3: Analyses of Co-Primary Endpoints (ITT Population)

	Number (%) of Subjects	
	Placebo N=68	***NUCALA* 300 mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0 weeks	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	3 (4)	9 (13)
24 to <36 weeks	0	10 (15)
≥36 weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
Subjects in Remission at Weeks 36 and 48	2 (3)	22 (32)
Odds ratio (mepolizumab/placebo)		16.74
95% CI	---	3.61, 77.56
p-value	---	<0.001

An odds ratio >1 favours *NUCALA*

Subjects receiving *NUCALA* 300 mg achieved significantly greater accrued time in remission ($p<0.001$), and a higher proportion of subjects receiving *NUCALA* 300 mg were in remission at both Week 36 and Week 48 ($p<0.001$), compared to placebo using the secondary endpoint remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day.

Relapse

Compared with placebo, 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 hospitalisation), was significantly longer for subjects receiving *NUCALA* 300 mg ($p<0.001$) Additionally, subjects receiving *NUCALA* had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral Corticosteroid Reduction

Compared with placebo, subjects receiving *NUCALA* 300 mg had a lower average daily oral corticosteroid dose during Weeks 48 to 52 ($p <0.001$). In the *NUCALA* 300 mg group, 12 subjects (18%) were able to taper completely off OCS therapy compared with 2 subjects (3%) in the placebo group.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Study 205687 was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP.
Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.
Patients received a 100 mg dose of *NUCALA*, or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

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The demographics and baseline characteristics of patients in study 205687 are provided in Table 4 below:

Table 4 Demographics and baseline characteristics in CRSwNP

	N = 407
Age (y) of patients, mean (SD)	49 (13)
Female, n (%)	143 (35)
White, n (%)	379 (93)
Duration (y) of CRSwNP, mean (SD)	11.4 (8.39)
Patients with >= 1 previous surgery, n (%)	407 (100)
Patients with >= 3 previous surgeries, n (%)	124 (30)
OCS use for NP (≥1 course) in past 12 months, n (%)	197 (48)
Total endoscopic NP score[a b c], mean (SD), maximum score = 8	5.5 (1.29)
Nasal obstruction VAS score[a d], mean (SD), maximum score = 10	9.0 (0.83)
Overall VAS symptom score[a d], mean (SD), maximum score = 10	9.1 (0.74)
SNOT-22 total score[e], mean (SD), range 0-110	64.1 (18.32)
Composite VAS symptoms score[a], mean (SD), maximum score = 10	9.0 (0.82)
Loss of smell VAS score[a,d], mean (SD), maximum score = 10	9.7 (0.72)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)
Geometric mean eosinophil count at baseline, cells/mcL (95% CI)	390 (360, 420)

CRSwNP = chronic rhinosinusitis with nasal polyps, SD = standard deviation, OCS = oral corticosteroid, NP = nasal polyps, VAS = visual analogue scale, SNOT-22 = Sino-Nasal Outcome Test, AERD = aspirin-exacerbated respiratory disease

[a] Higher scores indicate greater disease severity.

[b] As graded by independent blinded assessors

[c] NP score is the sum of scores from both nostrils (0-8 scale) where each nostril was graded (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle concha; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; 4=large polyps causing almost complete congestion/obstruction of the inferior meatus).

[d] Collected daily by patients on a 0 to 10 scale (0=none; 10=as bad as you can imagine).

[e] SNOT-22 is a health-related quality of life assessment tool and included 22 items in 6 domains of symptoms and impact associated with CRSwNP (nasal, non-nasal, ear/facial, sleep, fatigue, emotional consequences). Higher scores indicate worse health related quality of life.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. Patients who received *NUCALA* had significantly greater improvements (decreases) in total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo (see Table 4).

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Table 5: Analyses of co-primary endpoints (Intent To Treat population)

	Placebo (N=201)	*NUCALA* 100 mg SC (N=206)
Total Endoscopic Score at week 52 [a]		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value [b]		<0.001
Adjusted treatment difference in medians (95% CI) [c]		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52) [a]		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value [b]		<0.001
Adjusted treatment difference in medians (95% CI) [c]		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%) [d]	73 (36)	124 (60)

a) Subjects with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.

b) Based on Wilcoxon rank-sum test.

c) Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

d) A three-point improvement in Nasal Obstruction VAS has been identified as a meaningful within-patient change for this assessment.

All secondary endpoints were statistically significant and provided support for the co-primary endpoints. The key secondary endpoint was the time to first NP surgery up to Week 52 (see Figure 1). Data from the other secondary endpoints are presented in Table 6.

Time to First NP surgery

Across the 52-week treatment period, patients in the *NUCALA* group had a lower probability of undergoing NP surgery than patients in the placebo group (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [polypectomy] in the nasal cavity).

By Week 52, 18 patients (9%) in the *NUCALA* group had undergone NP surgery compared with 46 patients (23%) in the placebo group.

Patients who received *NUCALA* had an increase in the time to first NP surgery compared with placebo. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with *NUCALA* compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; unadjusted/adjusted p=0.003), a post-hoc analysis showed a 61% reduction in the odds of surgery (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

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Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps surgery

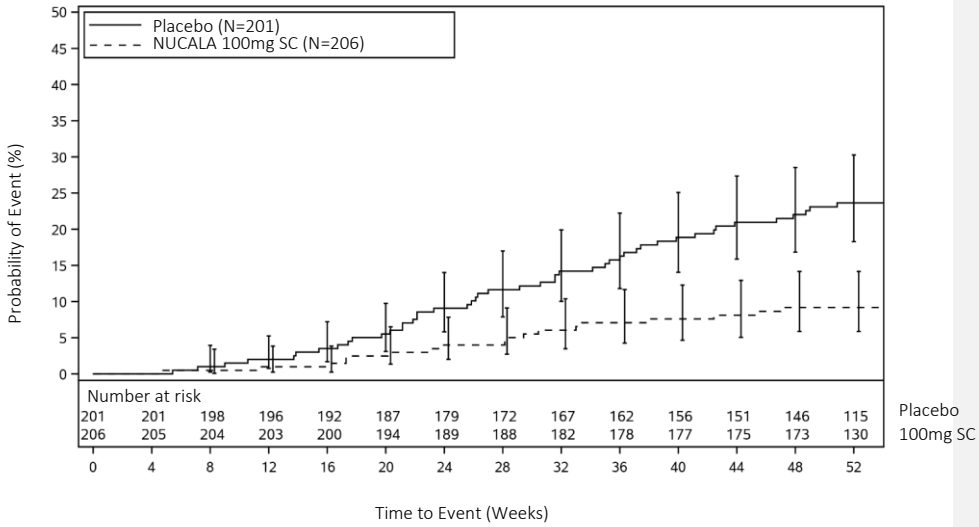

Table 6: Results of other secondary endpoints in the Intent to Treat population

	Placebo (N=201)	*NUCALA* (N=206)
Overall VAS Score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%)	40	64
SNOT-22 Total Score at Week 52 [a, g]		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-16.49 (-23.57, -9.42)
>=28-point improvement (%)[g]	32	54

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Patients Requiring Systemic Steroids for Nasal Polyps up to Week 52		
Number of patients with ≥1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) [e]		0.58 (0.36, 0.92)
Unadjusted/adjusted p-value [c, e]		0.020/0.020
Composite VAS Score - Nasal Symptoms (Weeks 49-52) [a,f]		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-2.68 (-3.44, -1.91)
>=2-point improvement (%)[h]	40	66
Loss of Smell VAS Score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-0.37 (-0.65, -0.08)
>=3-point improvement (%)[h]	19	36

[a] Patients with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.
[b] Based on Wilcoxon rank-sum test.
[c] Multiplicity controlled through testing of secondary endpoints following a pre-defined hierarchy.
[d] Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
[e] Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total ENP score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.
[f] Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.
[g] Improvement was seen in all 6 domains of symptoms and impact associated with CRSwNP.
[h] Threshold for improvement for each endpoint, has been identified as a meaningful within-patient change for this assessment.

Endpoints in patients with Asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received *NUCALA* 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for *NUCALA* 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

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Pharmacokinetics

Following subcutaneous dosing in subjects with moderate/severe asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Mepolizumab pharmacokinetics were consistent in subjects with asthma, COPD or EGPA. Subcutaneous administration of NUCALA 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. In a PK comparability study conducted in healthy subjects, following administration of a single 100 mg subcutaneous dose, mepolizumab pharmacokinetics were comparable between formulations.

Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration (T_{max}) ranging from 4 to 8 days.

Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single intravenous administration of mepolizumab to patients with asthma, the mean volume of distribution is 55 to 85 mL/kg.

Metabolism

Mepolizumab is a humanized IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life (t1/2) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special Patient Populations

The population pharmacokinetics of mepolizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for race or gender.

Elderly patients (>65 years old)

No formal studies have been conducted in elderly patients. However, in the population pharmacokinetic analysis, there was no indication of an effect of age on the pharmacokinetics of mepolizumab.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Pre-clinical Safety Data

Carcinogenesis/mutagenesis

As mepolizumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

Reproductive Toxicology

Fertility

No impairment of fertility was observed in a fertility and general reproduction toxicity study in mice performed with an analogous antibody that inhibits IL-5 in mice. This study did not include a littering or functional F1 assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/foetal and postnatal development (including immune function) of the offspring. Examinations for internal or skeletal malformations were not performed. Data in cynomolgus monkeys demonstrate that mepolizumab crosses the placenta. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers for several months post-partum and did not affect the immune system of the infants.

Animal toxicology and pharmacology

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in monkeys. Intravenous and subcutaneous administration to monkeys was associated with reductions in peripheral and lung eosinophil counts, with no toxicological findings.

Eosinophils have been associated with immune system responses to some parasitic infections. Studies conducted in mice treated with anti-IL-5 antibodies or genetically deficient in IL-5 or eosinophils have not shown impaired ability to clear parasitic infections.

PHARMACEUTICAL INFORMATION

List of Excipients

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Sucrose

Sodium phosphate dibasic heptahydrate

Citric acid monohydrate

Polysorbate 80

EDTA disodium dehydrate

Water for injection

Shelf Life

The expiry date is indicated on the packaging.

Storage

Store in refrigerator (2-8ºC). Do not freeze.

Protect from light. Store in the original carton until use.

If necessary, the pre-filled pen and pre-filled syringe can be removed from the refrigerator and kept in the unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

The pre-filled pen or pre-filled syringe must be administered within 8 hours once the pack is opened. Discard if not administered within 8 hours.

Nature and Contents of Container

Solution for injection in pre-filled pen (auto-injector)

1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled as an auto-injector.

NUCALA is supplied in a pack containing one single use pre-filled pen (auto-injector).

Solution for injection in pre-filled syringe (safety syringe)

1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled with a needle guard.

NUCALA is supplied in a pack containing one single use pre-filled syringe (safety syringe).

Not all dose forms or container types may be distributed in Malaysia.

Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

Special precautions for disposal and other handling

Before administration, the solution should be inspected visually. The liquid should be clear to opalescent, colourless to pale yellow to pale brown. If the solution is cloudy, discoloured or contains particles, the solution should not be used.
After removing the pre-filled pen or pre-filled syringe from the refrigerator, allow the pen or syringe to reach room temperature for at least 30 minutes before injecting *NUCALA*.

Comprehensive instructions for subcutaneous administration of *NUCALA* in a pre-filled pen or pre-filled syringe are provided at the end of the package leaflet.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured and released by:
Glaxo Operations UK Ltd.
(Trading as Glaxo Wellcome Operations)
Harmire Road, Barnard Castle,
DL12 8DT, United Kingdom.

Version number: 032
Reference: GDS16/IPI06 & EUSPC 24 Jun 2022
Date of local revision: ~~12 December~~~~14 May~~ 8 February 20254

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INSTRUCTIONS FOR USE

Solution for injection in pre-filled pen (auto-injector)

NUCALA pre-filled pen (auto-injector)

(*mepolizumab*)

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled pen. Failure to follow these instructions may affect proper function of the pre-filled pen. You should also receive training on how to use the pre-filled pen. *NUCALA* pre-filled pen is for use **under the skin only** (subcutaneous).

How to store *NUCALA*

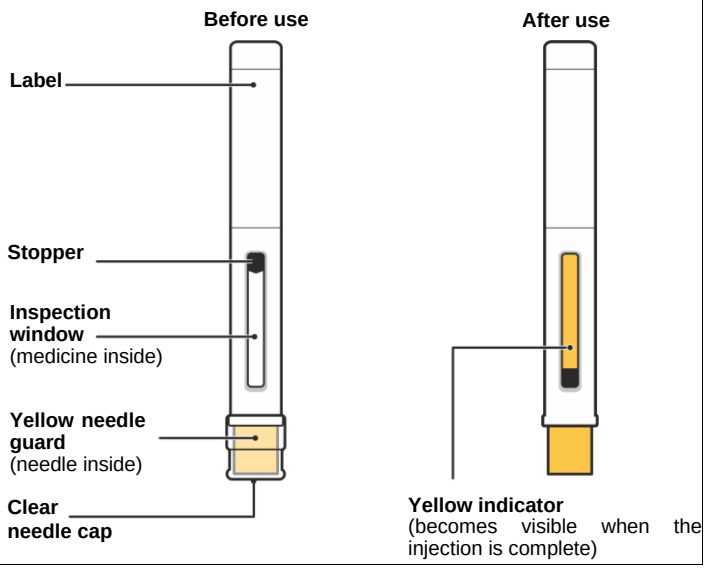
- Keep refrigerated before use.
- Do not freeze
- Keep the pre-filled pen in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled pen may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled pen away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use *NUCALA*

The pre-filled pen should be used only once and then discarded.

- **Do not** share your *NUCALA* pre-filled pen with another person.
- **Do not** shake the pen.
- **Do not** use the pen if dropped onto a hard surface.
- **Do not** use the pen if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled pen

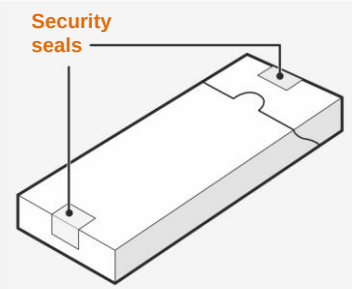


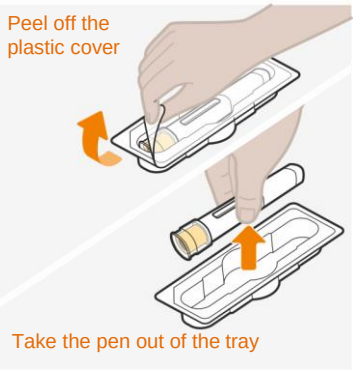
Prepare

1.Get ready what you need

- Find a comfortable, well-lit and clean surface. Make sure you have within reach:
  - *NUCALA* pre-filled pen
  - Alcohol wipe (not included)
  - Gauze pad or cotton wool ball (not included)

2. Take out your pre-filled pen



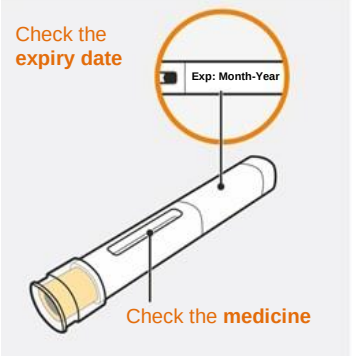


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the pen, carefully take it out of the tray.
- Place the pen on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the pen if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

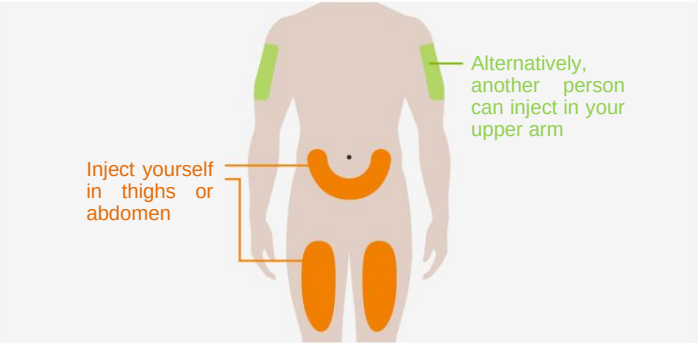
3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the pen.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the pen in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the pen if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step.

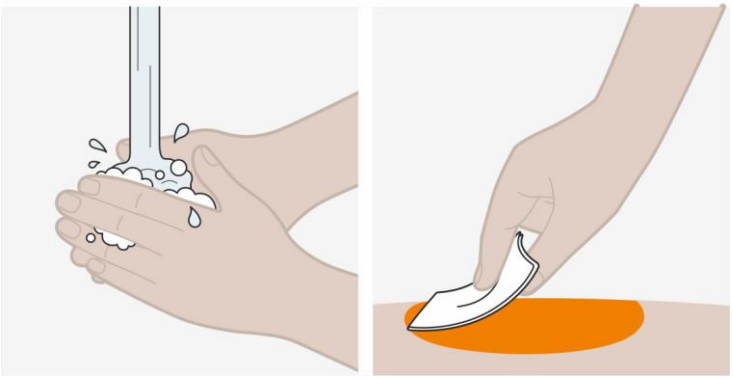
4. Choose your injection site



- You can inject *NUCALA* into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

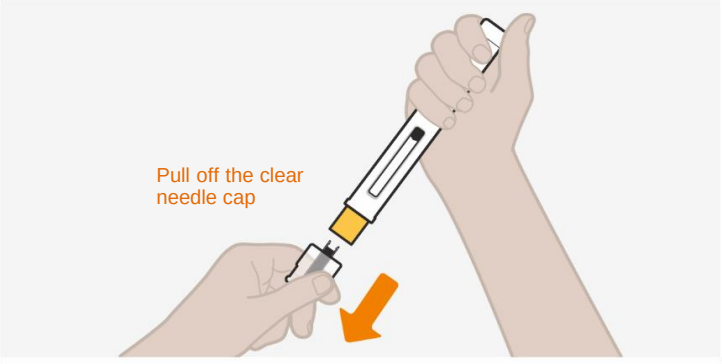


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the clear needle cap

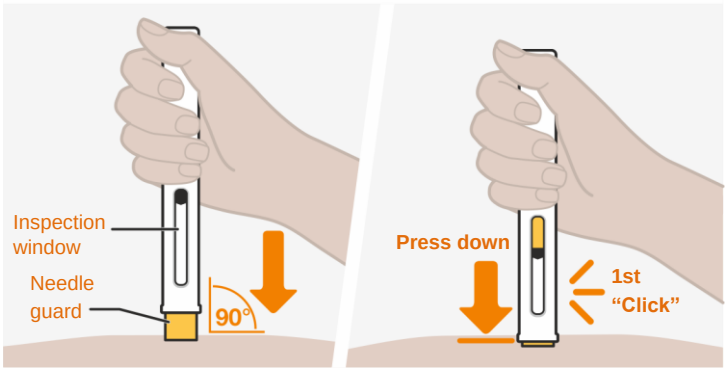


- Remove the clear needle cap from the pen by firmly pulling it straight off.
- Do not worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not touch the yellow needle guard with your fingers. This could activate the pen too soon and may cause a needle injury.

After removal, **do not** put the needle cap back onto the pen, as it may accidentally start the injection.

7. Start your injection

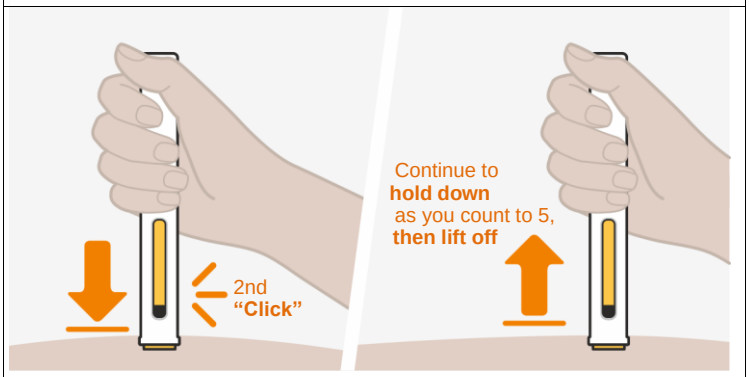


- Hold the pen with its inspection window facing towards you, so you can see it, and with the yellow needle guard facing down.
- Place the pen straight onto your injection site with the yellow needle guard flat against the surface of your skin, as shown.
- To start your injection, push the pen down all the way and keep it held down against your skin. The yellow needle guard will slide up into the pen.
- You should hear the 1st "click" to tell you your injection has started.
- The yellow indicator will move down through the inspection window as you receive your dose.

Do not lift the pen from your skin at this stage, as that may mean you don't get your full dose of medicine. Your injection may take up to 15 seconds to complete.

Do not use the pen if the yellow needle guard doesn't slide up as described. Dispose of it (see Step 9), and start again with a new pen.

8. Hold the pen in place to complete your injection



- Continue to hold the pen down until you hear the 2nd "click", and the stopper and yellow indicator have stopped moving and fill the inspection window.
- Continue to hold the pen in place while you count to 5. Then lift the pen away from your skin.
- If you do **not** hear the 2nd "click":
  - Check that the inspection window is filled with the yellow indicator.
  - If you are not sure, hold the pen down for another 15 seconds to make sure the injection is complete.

Do not lift the pen until you are sure you have completed your injection.

- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.

Do not rub your injection site.

Dispose

9. Dispose of the used pen

- Dispose of the used pen and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used pens and needle caps out of the sight and reach of children.**

INSTRUCTIONS FOR USE

Solution for injection in pre-filled syringe (Safety syringe)

NUCALA pre-filled syringe (Safety syringe)

(mepolizumab)

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. NUCALA pre-filled syringe is for use **under the skin only** (subcutaneous).

How to store *NUCALA*

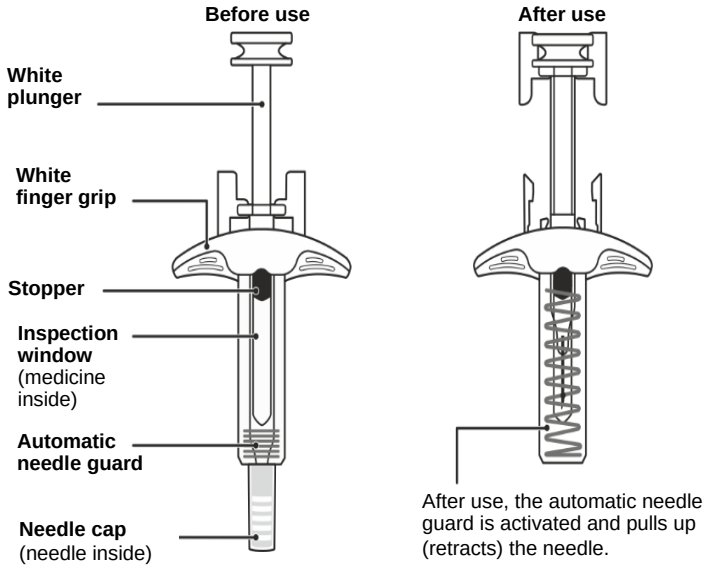
- Keep refrigerated before use.
- Do not freeze.
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled syringe away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use *NUCALA*

The pre-filled syringe should be used only once and then discarded.

- **Do not** share your *NUCALA* pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled syringe

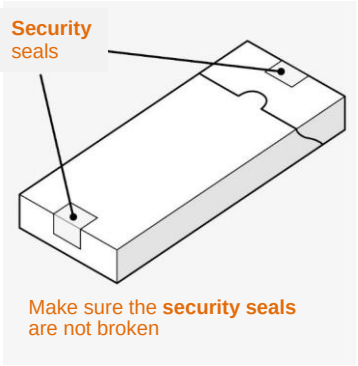


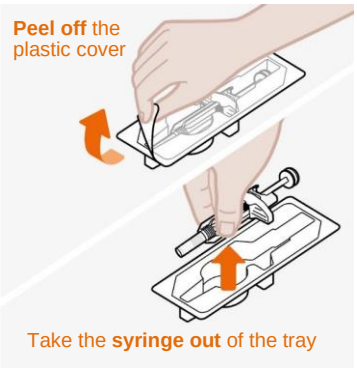
Prepare

1. Get ready what you need

- Find a comfortable, well-lit and clean surface. Make sure you have within reach:
  - *NUCALA* pre-filled syringe
  - Alcohol wipe (not included)
  - Gauze pad or cotton wool ball (not included)

2. Take out your pre-filled syringe

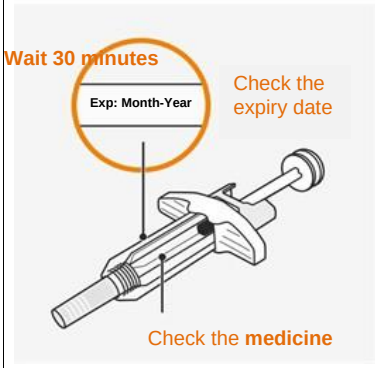




- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.
Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use

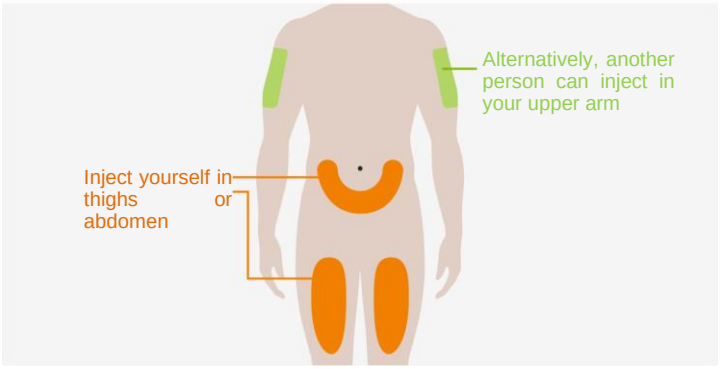


- Check the expiry date on the label of the syringe.

- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the syringe in a microwave, hot water, or direct sunlight. **Do not** inject if the solution looks cloudy or discoloured, or has particles. **Do not** use the syringe if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step

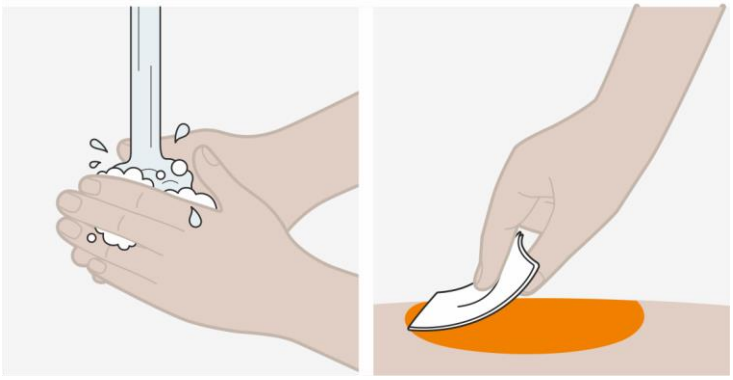
4. Choose your injection site



- You can inject *NUCALA* into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete you dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

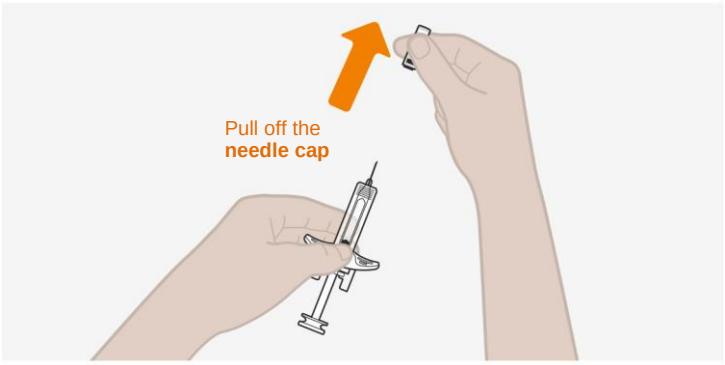


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.

- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not let the needle touch any surface.

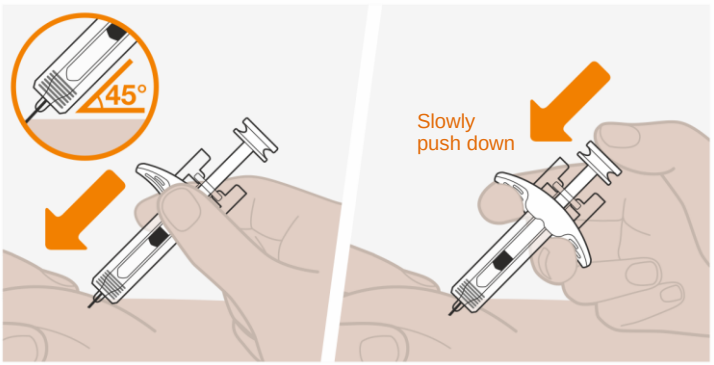
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not receive your full dose.

Do not expel any air bubbles from the syringe.

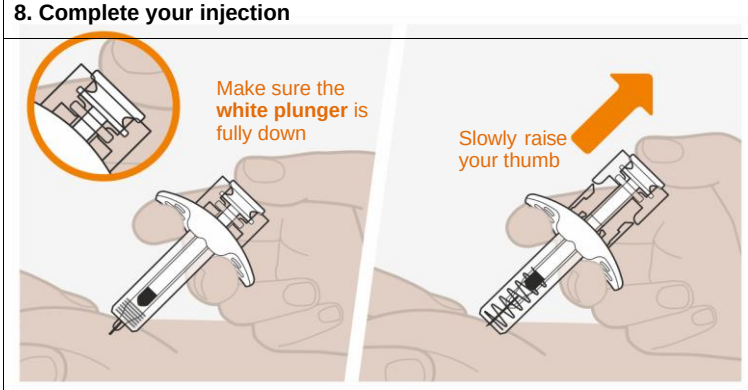
Do not put the needle cap back onto the syringe. This could cause a needle injury.

7. Start your injection



- Use your free hand to pinch the skin around your injection site. Keep the skin pinched throughout your injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject your full dose.

8. Complete your injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
  - You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub your injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used syringes and needle caps out of the sight and reach of children.**