For the use only of Registered Medical Specialists experienced in treating the diseases for which drug is approved

NUCALA 100 mg

1. GENERIC NAME

Mepolizumab Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NUCALA 100 mg solution for injection in pre-filled pen

Each 1 ml pre-filled pen contains 100 mg of mepolizumab.

NUCALA 100 mg solution for injection in pre-filled syringe

Each 1 ml pre-filled syringe contains 100 mg of mepolizumab.

List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Polysorbate 80
EDTA disodium dihydrate
Water for injection

3. DOSAGE FORM AND STRENGTH

Solution for injection

100 mg/mL

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Severe Eosinophilic Asthma
NUCALA is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients (see section *5.2. Pharmacodynamic properties*).

Eosinophilic granulomatosis with polyangiitis (EGPA)
NUCALA is indicated as an add-on treatment for adult patients with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)
NUCALA is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see section *5.2. Pharmacodynamic properties*).

4.2. Posology and Method of Administration

NUCALA should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, EGPA or HES.

Posology

Severe Eosinophilic Asthma

Adults

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.

EGPA

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

NUCALA is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and improvement of symptom control.
Patients who develop life-threatening manifestations of EGPA should also be evaluated for the need for continued therapy, as *NUCALA* has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

NUCALA is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and level of symptom control.
Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as *NUCALA* has not been studied in this population.

Special populations

Elderly patients

No dose adjustment is required for elderly patients (see section *5.3. Pharmacokinetic properties*).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section *5.3. Pharmacokinetic properties*).

Method of administration

The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only.

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.

For self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject *NUCALA* into the upper arm.

For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section *2. Qualitative and Quantitative Composition*

4.4. Special Warnings and Precautions for Use

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

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

Corticosteroids

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

Hypersensitivity and administration-related reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances

have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment (see section *4.8.Undesirable Effects*). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Organ threatening or life-threatening EGPA

NUCALA has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section *4.2. Posology and Method of Administration*).

Life-threatening HES

NUCALA has not been studied in patients with life-threatening manifestations of HES (see section *4.2 Posology and Method of Administration*).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially "sodium-free".

4.5. Drug Interactions

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

4.6. Use in Special Populations

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.

Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section *6. Nonclinical Properties*). The potential for harm to a human fetus is unknown.

As a precautionary measure, it is preferable to avoid the use of *NUCALA* during pregnancy. Administration of *NUCALA* to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

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

A decision must be made whether to discontinue breast-feeding or to discontinue *NUCALA* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see section *6. Nonclinical Properties*).

4.7. Effects on Ability to Drive and Use Machines

NUCALA has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects

Summary of the safety profile

Severe eosinophilic asthma

In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

EGPA
In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES
In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions

Severe eosinophilic asthma and EGPA

The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies with frequencies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n= 263), in patients with EGPA receiving mepolizumab 300 mg SC (n=68) and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years).

HES

In a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), no additional adverse reactions were identified to those reported in the severe eosinophilic asthma studies.
The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

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); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse Reactions**	**Frequency**
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and 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	Administration-related reactions (systemic non allergic)*** Local injection site reactions Pyrexia	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 section *4.4. Special warnings and precautions for use.*
** From spontaneous post marketing reporting.
*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reaction

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic nonallergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

EGPA

In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

4.9 Overdose

Single doses of up to 1,500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. 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.

5. PHARMACOLOGICAL PROPERTIES

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

5.1. Mechanism of Action

Mepolizumab 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. Mepolizumab 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 signaling and reducing the production and survival of eosinophils.

5.2. Pharmacodynamic Properties

Pharmacodynamic effects

Severe eosinophilic asthma

In patients with severe refractory eosinophilic asthma, 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 blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

In adults, this magnitude of reduction was observed within 4 weeks of treatment.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/µL (n=64) at week 52. There was a geometric mean reduction of 83% compared to placebo and this magnitude of reduction was observed within 4 weeks of treatment.

HES

In patients with HES, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1460 (n=54) to 70 cells/µL (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, 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 adult and adolescents with severe refractory eosinophilic asthma treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults 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.

Neutralising antibodies were detected in one subject with severe refractory eosinophilic asthma and in no patients with 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.

Clinical efficacy

Severe eosinophilic asthma

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory 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 patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting beta$_2$ -adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV_1 was 60%. Patients continued to receive their existing asthma medicine during the studies**.**

For the oral corticosteroid-sparing study MEA115575, a total of 135 patients were enrolled (55% were female; mean age of 50 years) who were being treated daily with OCS (5-35 mg per day), and high-dose ICS plus an additional maintenance medicine.

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 with severe refractory eosinophilic asthma, mepolizumab significantly reduced clinically significant asthma exacerbations (defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits) when administered in doses of 75 mg, 250 mg or 750 mg intravenously compared to placebo (see Table 1).

Table 1: Frequency of clinically significant exacerbations at week 52 in the intent to treat population

	Intravenous Mepolizumab			**Placebo**
	75mg n=153	**250mg n=152**	**750mg n=156**	**n= 155**
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61(0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

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 mepolizumab as add-on therapy in 576 patients with severe refractory eosinophilic asthma defined as peripheral blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or greater than or equal to 300 cells/µL within the past 12 months.

Patients received mepolizumab 100 mg administered subcutaneously, mepolizumab 75 mg administered intravenously or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint was the frequency of clinically significant exacerbations of asthma and the reductions for both mepolizumab treatment arms compared to placebo were statistically significant ($p<0.001$). Table 2 provides the results of the primary and secondary endpoints for patients treated with subcutaneous mepolizumab or placebo.

Table 2: Results of primary and secondary endpoints at week 32 in the intent to treat population (MEA115588)

	Mepolizumab 100 mg (subcutaneous) **N=194**	**Placebo** **N= 191**
Primary endpoints		
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		
Exacerbation 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		
Baseline (SD)	1730 (659)	1860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11,184)	

	Mepolizumab 100 mg (subcutaneous) N=194	Placebo N= 191
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19.5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

Table 3 shows the results of a combined analysis of the two exacerbation studies (MEA112997 and MEA115588) by baseline blood eosinophil count. The rate of exacerbations in the placebo arm increased with increasing baseline blood eosinophil count. The reduction rate with mepolizumab was greater in patients with higher blood eosinophil counts.

Table 3: Combined analysis of the rate of clinically significant exacerbations by baseline blood eosinophil count in patients with severe refractory eosinophilic asthma

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/µL		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
150 to <300 cells/µL		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.72 (0.47,1.10)	---
300 to <500 cells/µL		
n	109	76
Exacerbation rate per year	1.02	1.64
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
>500 cells/µL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of ≥150/μL at baseline or a blood eosinophil count of ≥300/μL in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicine during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

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

The primary endpoint was the percent reduction in daily OCS dose (weeks 20-24), whilst maintaining asthma control by defined dose reduction categories (see Table 4). Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the prednisone dose from the end of the optimisation phase. The comparison between mepolizumab and placebo was statistically significant (p=0.008).

Table 4: Results of the primary and secondary endpoints in MEA115575

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	**Placebo N= 66**
Primary endpoint		
Percent reduction in OCS from baseline (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 (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0. 414	
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	
Median % reduction in daily OCS dose 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	

Open-label extension studies in severe refractory eosinophilic asthma MEA115666 (COLUMBA), MEA115661 (COSMOS) and 201312 (COSMEX)

The long-term efficacy profile of *NUCALA* in severe refractory eosinophilic 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.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life- threatening EGPA were excluded from study MEA115921.
Patients either received a 300 mg dose of mepolizumab 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.

Remission

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

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 5).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

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

Table 5: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	**Mepolizumab 300mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0	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

	Number (%) of patients	
	Placebo N=68	**Mepolizumab 300mg N=68**
95% CI p-value	--- ---	2.68, 13.03 <0.001
Patients in remission at Weeks 36 and 48	2 (3)	22 (32)
Odds ratio (mepolizumab/placebo) 95% CI p-value	 --- ---	16.74 3.61, 77.56 <0.001

An odds ratio >1 favours mepolizumab. Remission: BVAS=0 and OCS dose ≤ 4mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg (p<0.001). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of ≤ 7.5 mg and ≤ 4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥12 years old with HES. Patients received 300 mg of mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.
Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥1000 cells/μL during screening. Patients who were FIP1L1-PDGFRα kinase-positive were excluded from the study.
The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥ 2 occasions).
The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 6).
Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 1 and Table 7).

Table 6: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo N= 54**
Proportion of patients who experienced a HES flare		
Patients with ≥1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH = Cochran-Mantel-Haenszel

Time to First Flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; p=0.002).

Figure 1: Kaplan Meier Curve for Time to First HES Flare

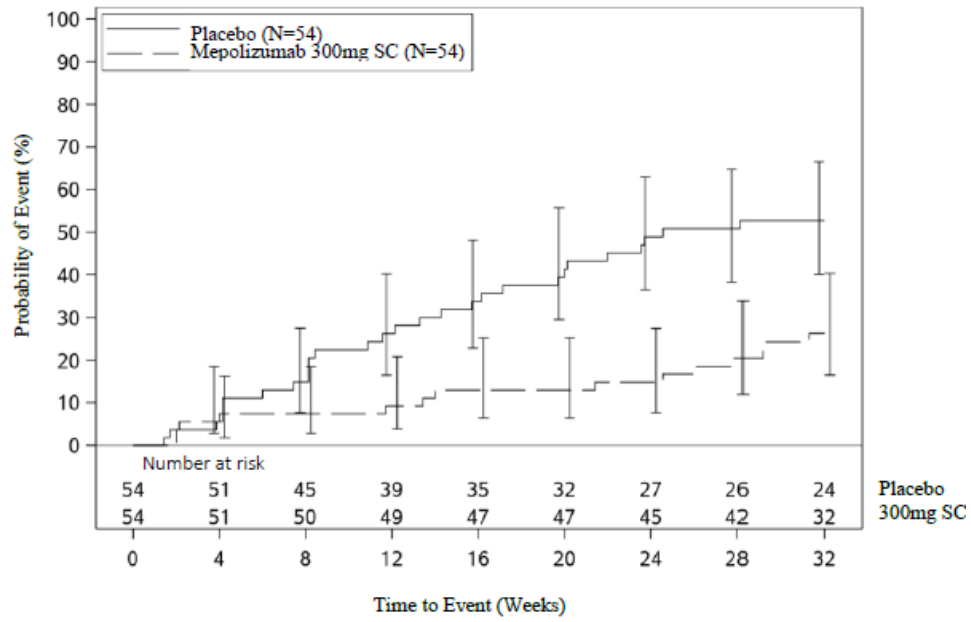


Table 7: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo N= 54**
HES flares during week 20 and up to and including week 32		
Patients with ≥1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value 0.02	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI)[a]	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	

	Mepolizumab 300 mg N= 54	Placebo N= 54
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32[b]		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

[a] rate ratio <1 favours mepolizumab.
[b] patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine
CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare. In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of ≥50% during Weeks 16 to 20.

5.3. 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. Subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. Following administration of a single 100 mg subcutaneous dose in healthy subjects, mepolizumab systemic exposure was 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 to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

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 populations

Elderly patients (≥65 years old)

There are limited pharmacokinetic data available in elderly patients (≥65 years old) across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12 to 82 years.

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 between 50-80 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and/or Pharmacology

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

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 are thought to be 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. The relevance of these findings for humans is unknown.

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 offspring assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal 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 crossed the placenta. Concentrations of mepolizumab were about 1.2-2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

7. DESCRIPTION

Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology

Mepolizumab Injection, 100 mg/mL, is a single-use, sterile liquid drug product (DP) in a clear glass pre-filled syringe (PFS) that delivers 100 mg of mepolizumab for subcutaneous administration. The mepolizumab DP primary container and closure consists of a 1 mL long Type 1 glass siliconized barrel with a staked 29G thin wall x 12.7 mm stainless steel needle with a thermoplastic elastomer needle shield covered by rigid plastic shield sealed with fluororesin coated bromobutyl rubber plunger stopper.

The PFS is assembled into either an autoinjector or a safety syringe device. The autoinjector is comprised of an opaque housing with a transparent clear inspection window, a yellow needle guard and a translucent cap.

Both injection devices are designed to deliver an injection volume of 1.0 mL (100 mg/mL).

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

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

8.2 Shelf life

36 months

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

NUCALA 100 mg solution for injection in pre-filled pen

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Pack sizes:
1 pre-filled pen
Multipack comprising 3 (3 packs of 1) pre-filled pens
Multipack comprising 9 (9 packs of 1) pre-filled pens

Not all pack-sizes may be marketed.

NUCALA 100 mg solution for injection in pre-filled syringe

1 ml solution in a Type 1 glass syringe with a fixed needle (stainless steel) and passive safety needle guard.

Pack sizes:
1 pre-filled syringe
Multipack comprising 3 (3 packs of 1) pre-filled syringes
Multipack comprising 9 (9 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

8.4 Storage and Handling Instructions

Store in refrigerator (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

If necessary, the pre-filled pen and pre-filled syringe can be removed from the refrigerator and kept in the unopened pack for up to 7 days at room temperature (up to 30°C), when protected from light. The pack should be discarded 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. The pack should be discarded if not administered within 8 hours.

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*.

Step by step instructions for using the pre-filled pen

Administer once every four 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. *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 pen away if it has been kept out of the refrigerator for more than 7 days.

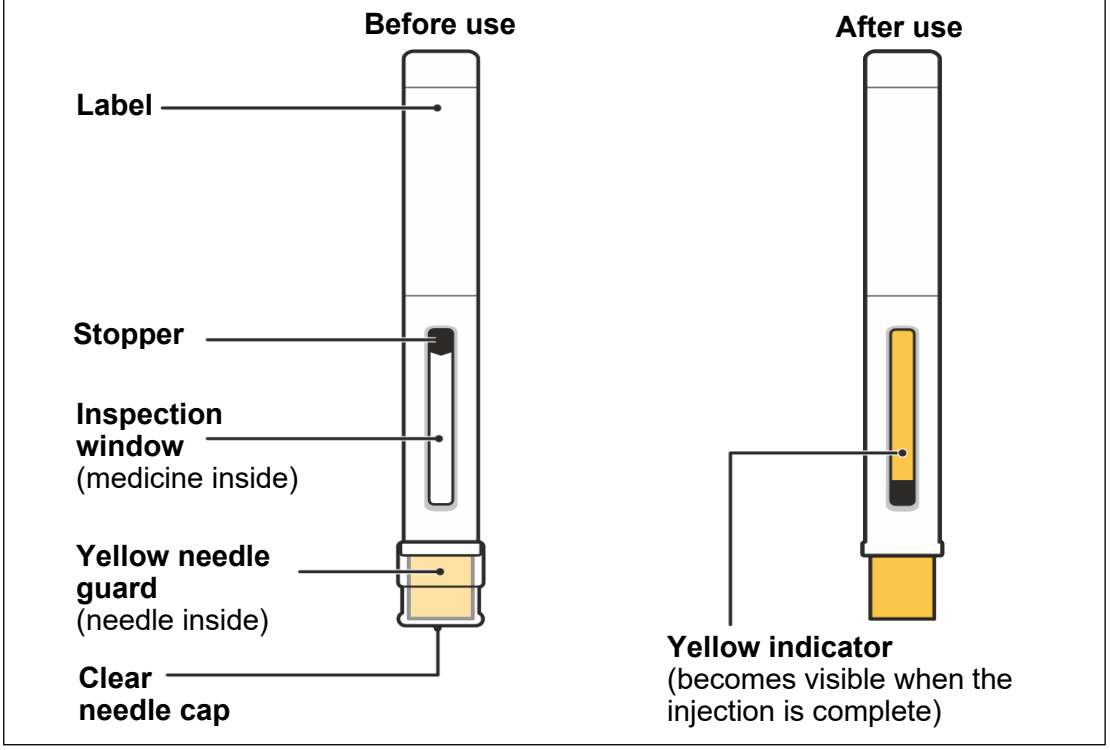
- Do not store it above 30°C.

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



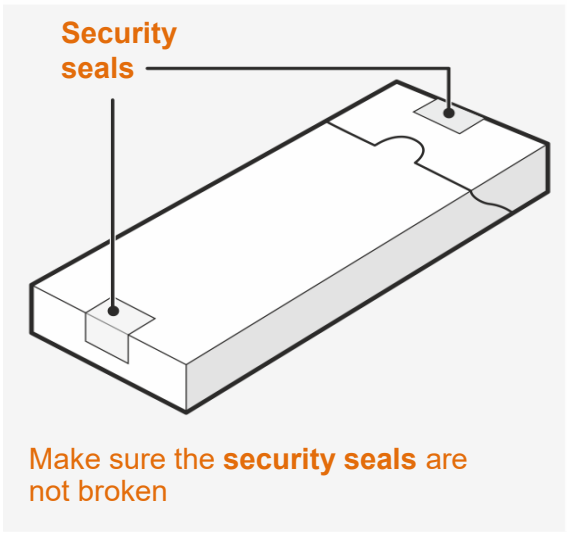
Prepare

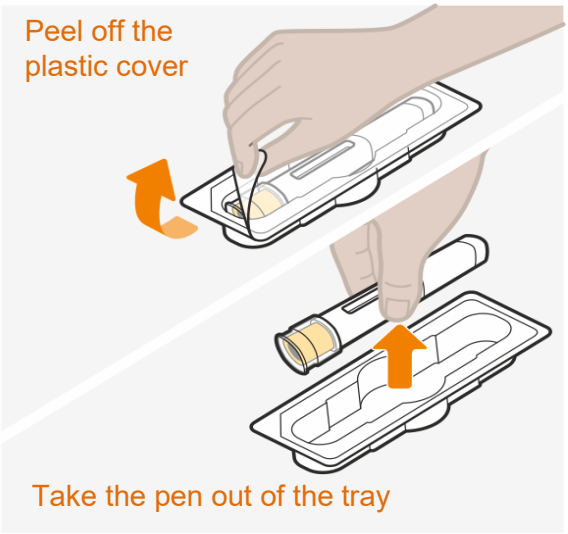
1.Get ready what you need

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



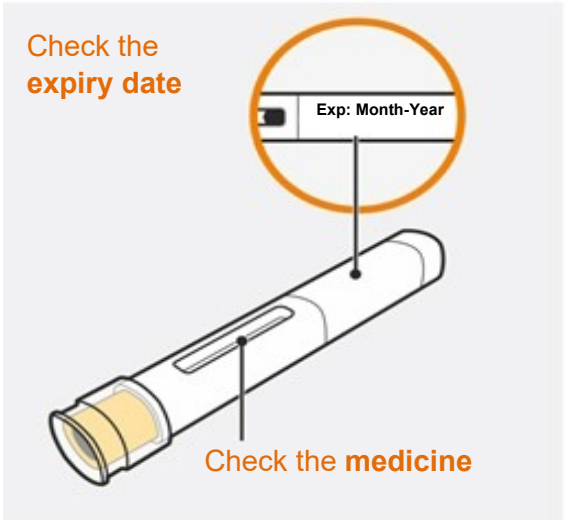


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the pen, carefully take it out of the tray.
- Place the pen on a clean, flat surface, at room temperature, away from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

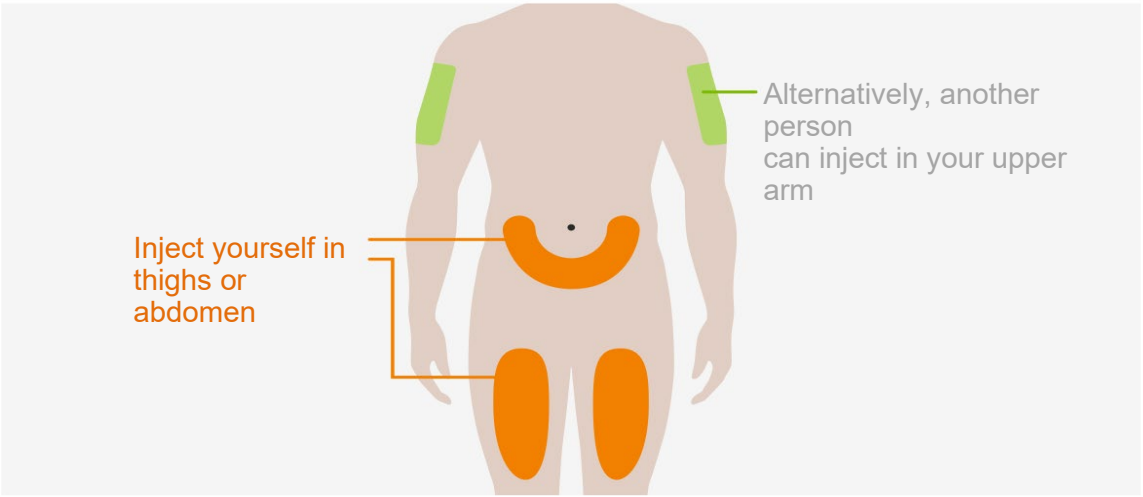
3. Inspect and wait 30 minutes before use



- 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.

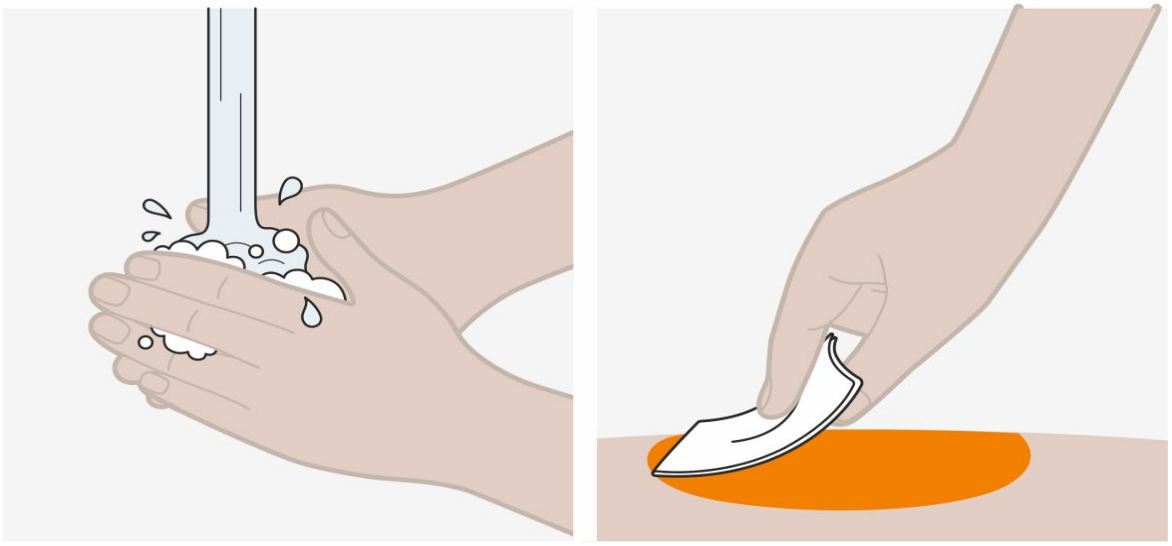
4. Choose your injection site



- 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

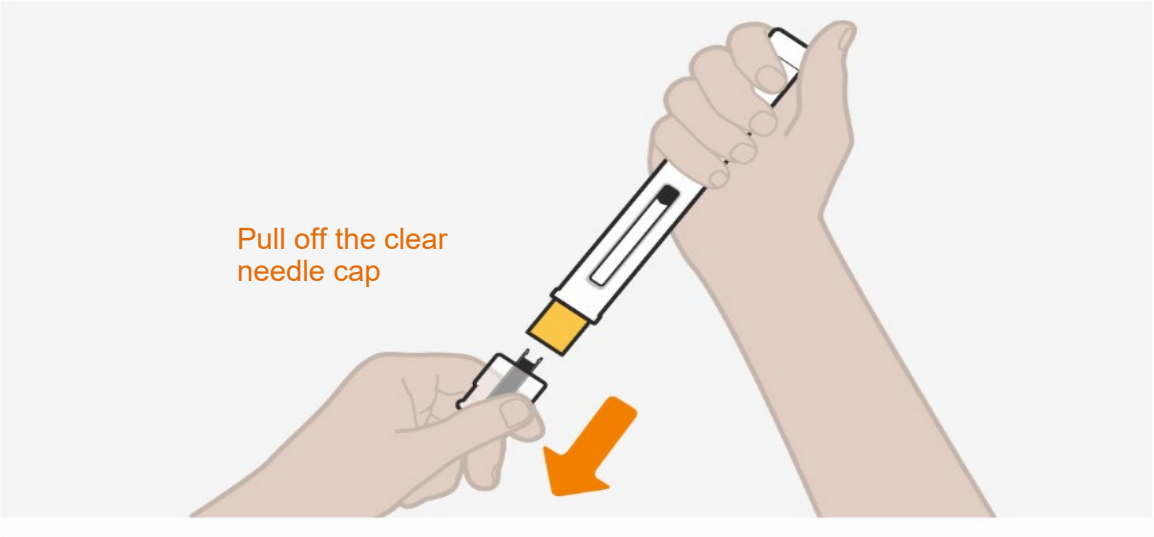


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

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

Inject

6. Remove the clear needle cap

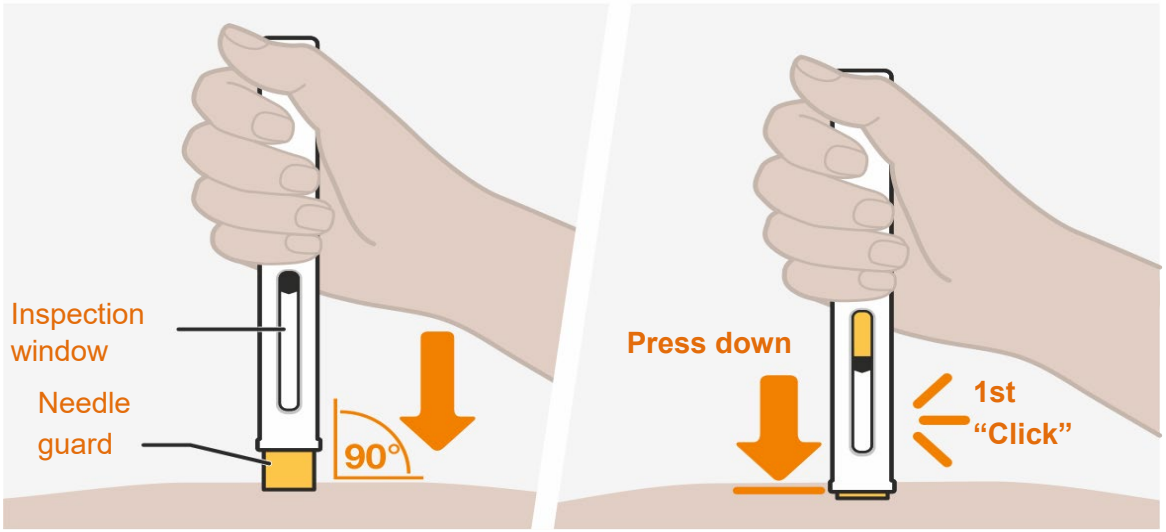


- Remove the clear needle cap from the pen by firmly pulling it straight off.
- Do not worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

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

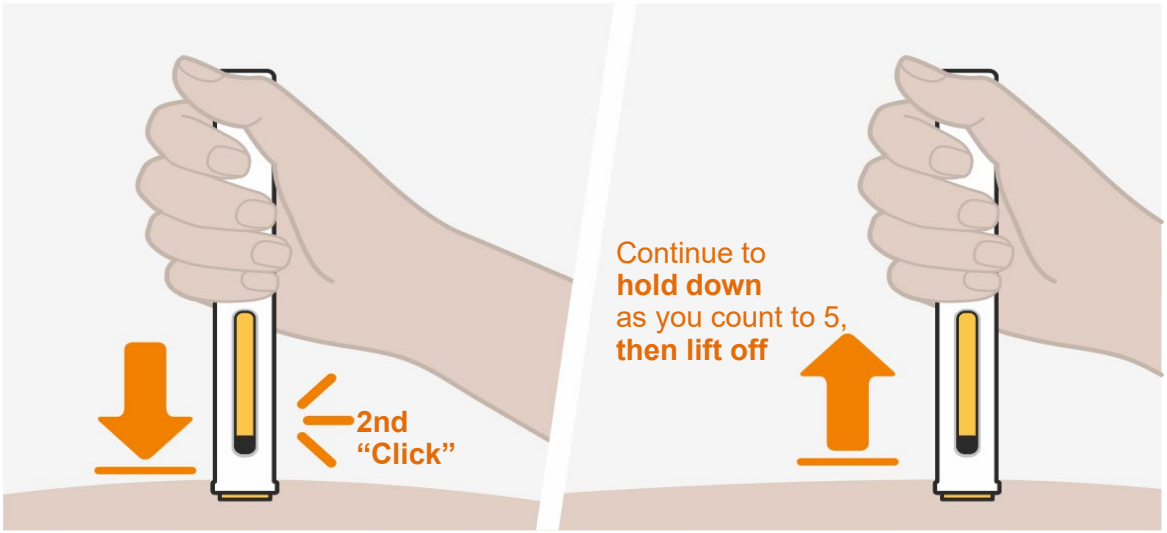


- Hold the pen with its inspection window facing towards you, so you can see it, and with the yellow needle guard facing down.
- Place the pen straight onto your injection site with the yellow needle guard flat against the surface of your skin, as shown.
- To start your injection, push the pen down all 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 for advice if necessary.
- **Keep your used pens and needle caps out of the sight and reach of children.**

Step by step instructions for using the pre-filled syringe

Administer once every four 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. *NUCALA* pre-filled syringe is for use **under the skin only** subcutaneous).

How to store *NUCALA*

- Keep refrigerated before use.

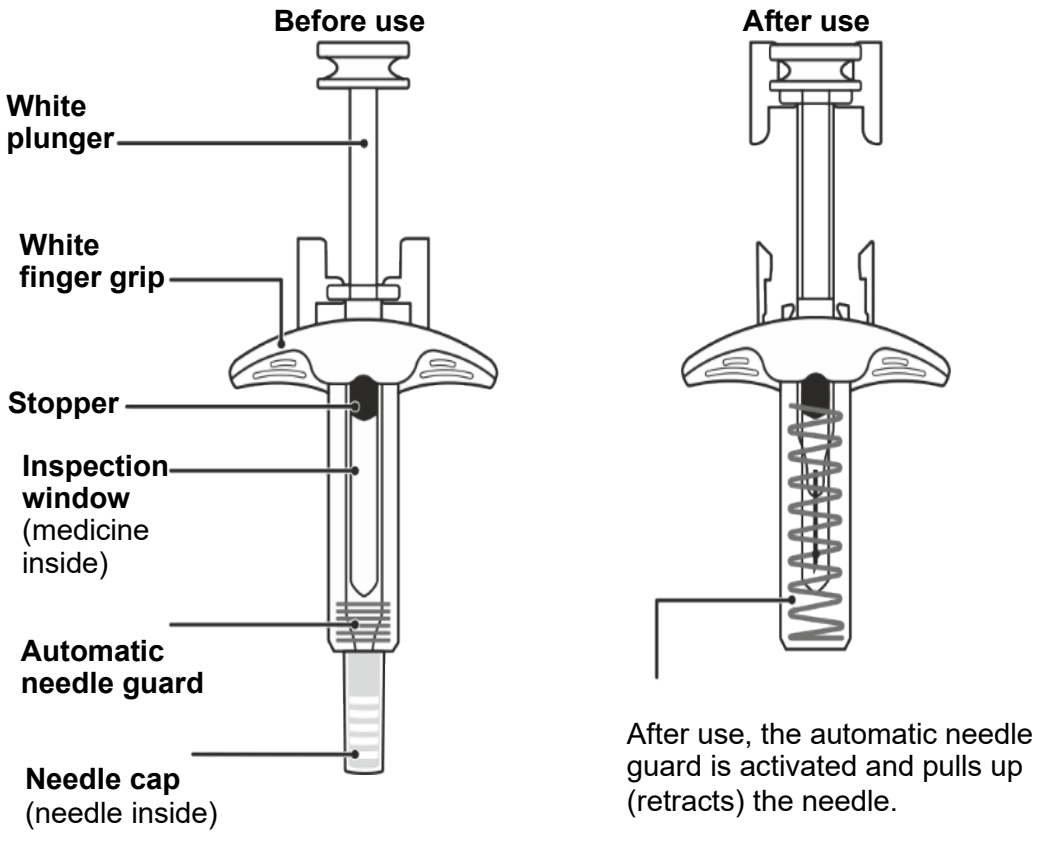
- Do not freeze
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled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



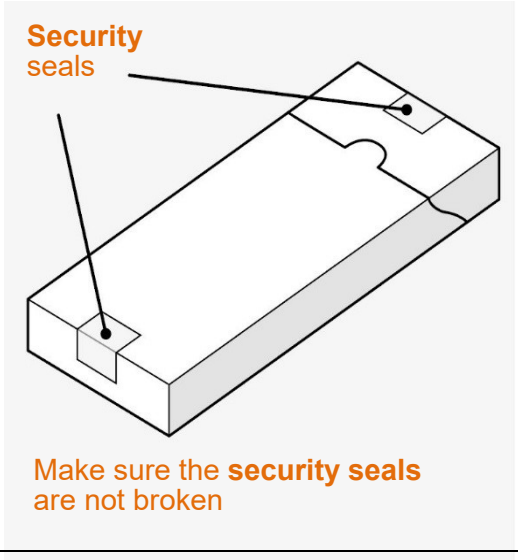
Prepare

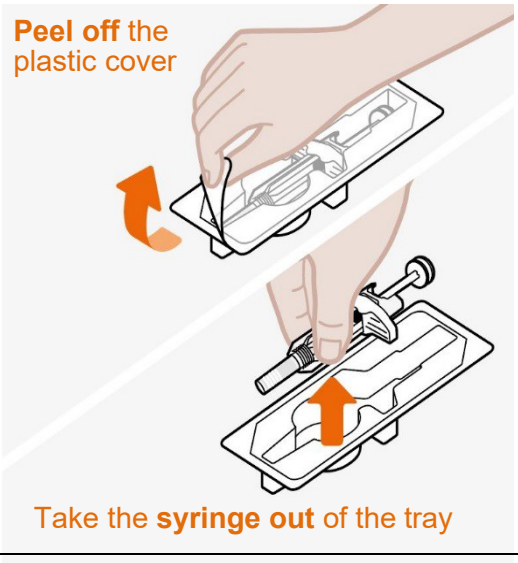
1. Get ready what you need

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

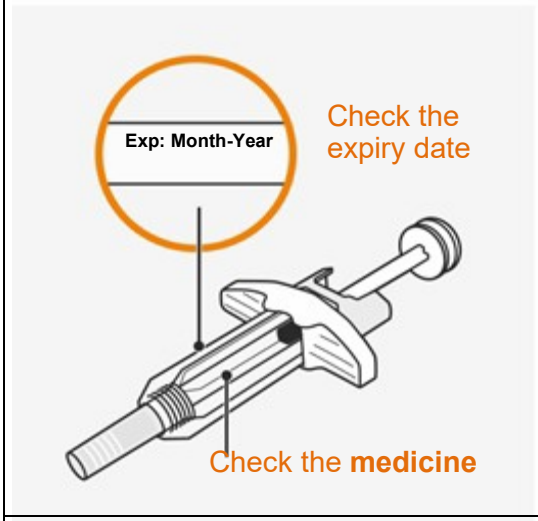


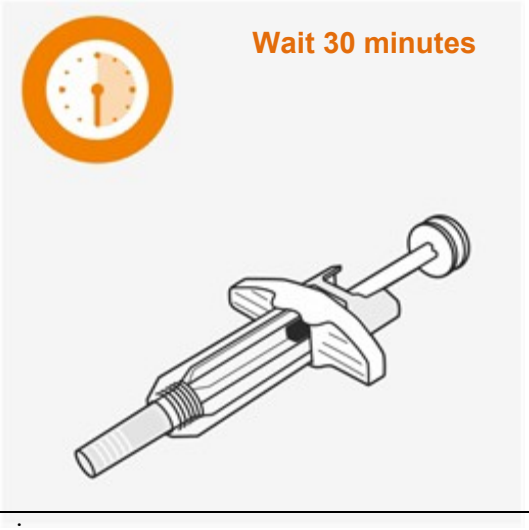


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away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

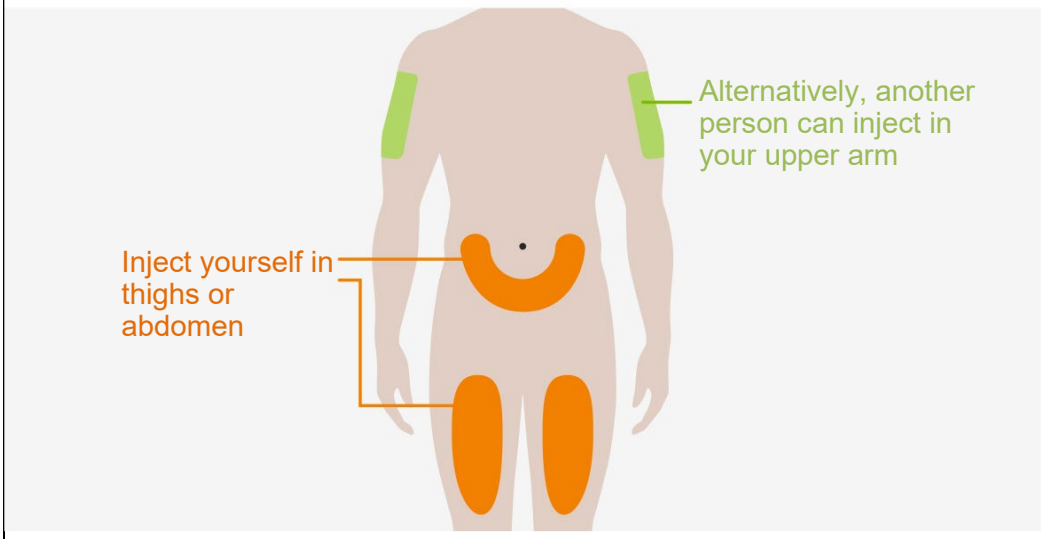




- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

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

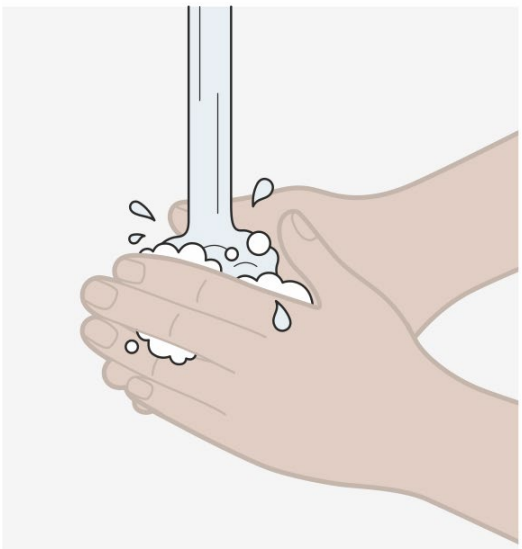
4. Choose your injection site

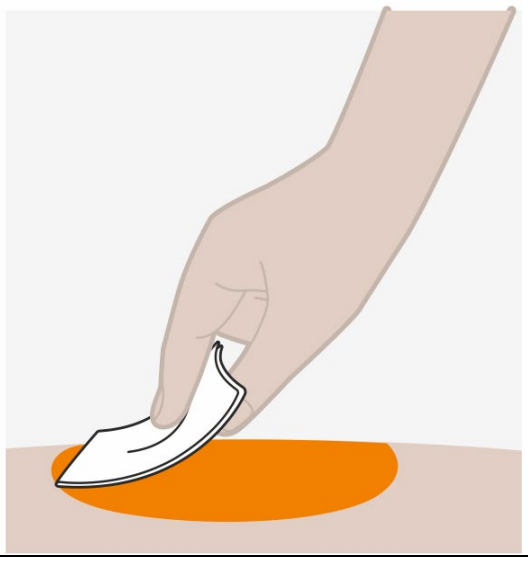


- You can inject *NUCALA* into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

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



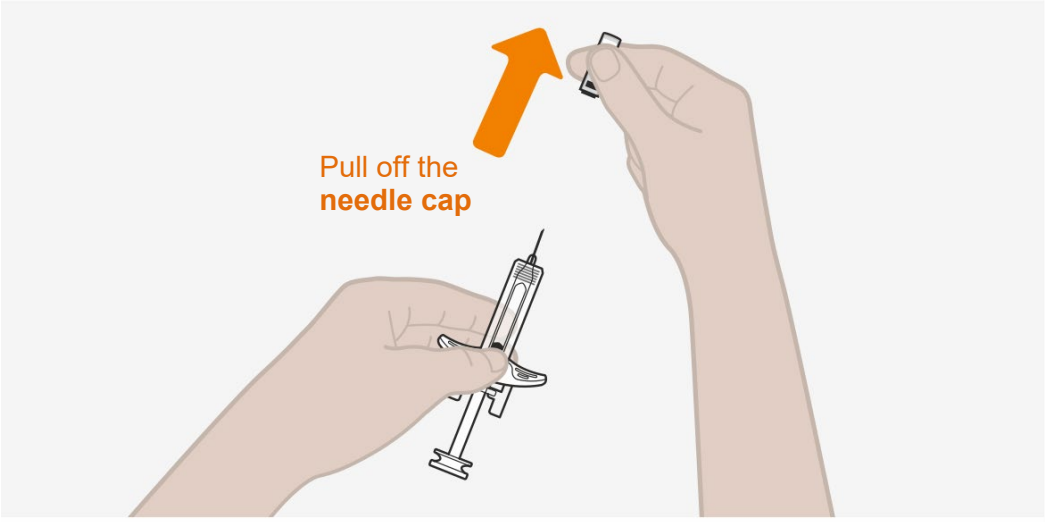


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

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

Inject

6. Remove the 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.

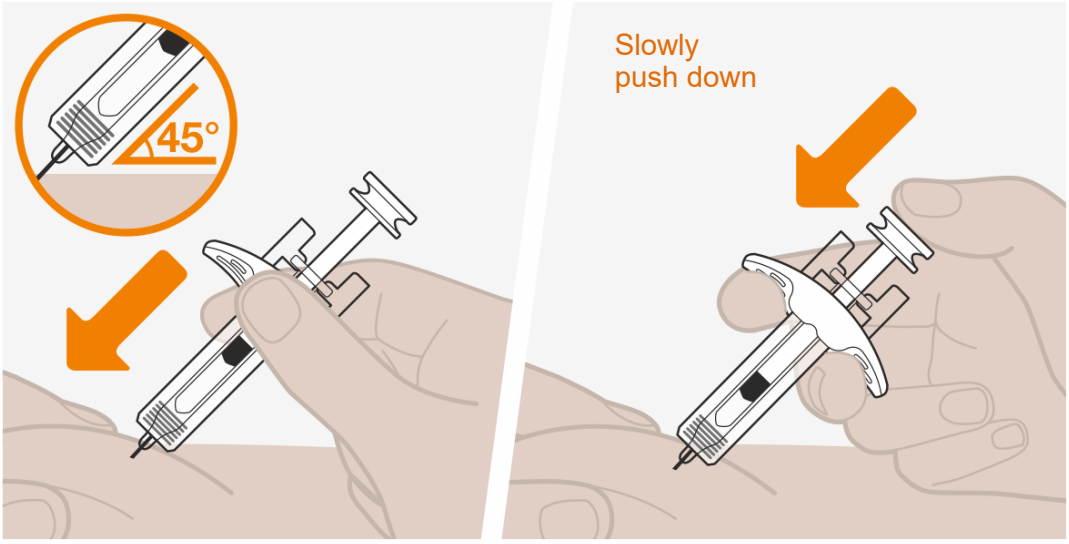
Do not touch the needle.

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.

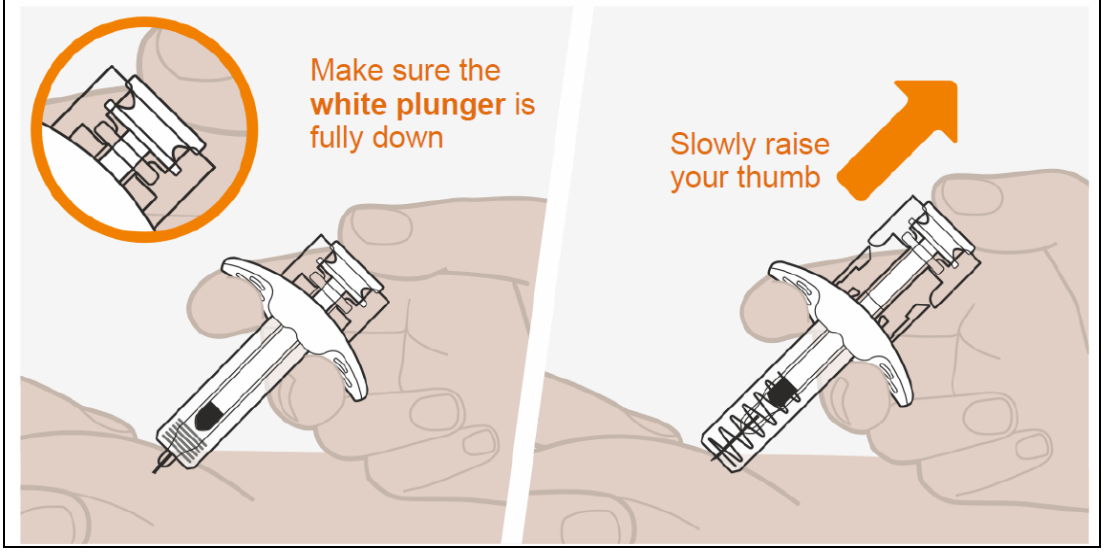
Do not put the needle cap back onto the syringe. This could cause a needle injury.

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 for advice if necessary.
- **Keep your used syringes and needle caps out of the sight and reach of children.**

9. PATIENT COUNSELING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *NUCALA 100 mg*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

M/s. Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations), Harmire Road, Barnard Castle, County Durham, DL12 8DT, United Kingdom

For further information please contact:

GlaxoSmithKline Pharmaceuticals Limited

Registered Office
Dr Annie Besant Road, Worli,
Mumbai 400030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Marketing Authorization Holder: GlaxoSmithKline Pharmaceuticals Limited, Dr. Annie Besant Road, Worli Mumbai 400 030, India.

Marketing Authorization Details: IMP-147/2018 dated 21-August-2020

12. DATE OF REVISION

03-JULY-2024

Version NUC-LI/PI/IN/2024/01

Adapted from EU SmPC dated 12 November 2021