NUCALA

Mepolizumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection in 40 mg/0.4 mL pre-filled syringe (safety syringe)

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

Each pre-filled syringe delivers 40 mg mepolizumab in 0.4 mL (40 mg/0.4 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.

CLINICAL INFORMATION

Indications

Severe Eosinophilic Asthma

NUCALA is indicated as add-on maintenance treatment of severe eosinophilic asthma in patients 6 to 11 years old (see *Clinical Studies*).

Dosage and Administration

Pharmaceutical form: Solution for injection in 40 mg/0.4 mL pre-filled syringe (safety syringe)

NUCALA should only be administered as a subcutaneous injection (see *Use and Handling and Instructions for Use*).

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

NUCALA must be administered by a healthcare professional or a caregiver. It may be administered by a caregiver if a healthcare professional determines that it is appropriate, and the caregiver is trained in injection techniques.

Populations

Severe Eosinophilic asthma

Children aged 6 to 11 years old:

The recommended dose is 40 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

The safety and efficacy of *NUCALA* have not been established in children less than 6 years of age.

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.

Asthma-related adverse events or exacerbations may occur during treatment with *NUCALA*. Patients should be instructed to seek medical advice if their asthma 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, 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). These reactions may occur for the first time after a long duration of treatment.

Parasitic Infections

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

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 *Non-Clinical Information*). 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.

Lactation

There are no data regarding the excretion of *NUCALA* in human milk. However, mepolizumab was excreted into the milk of cynomolgus 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 data

Severe 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) *NUCALA* 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	Common
	Lower respiratory tract infection	Common
	Urinary tract infection	Common
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
Immune system disorders	Hypersensitivity reactions (systemic allergic)*	Common
	Anaphylaxis**	Rare

System Organ Class	Adverse Reactions	Frequency
General disorders and administration site conditions	Pyrexia	Common
	Injection site reactions***	Common
	Administration-related reactions (systemic non-allergic)****	Common

*Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo. For examples of the associated manifestations reported and a description of the time to onset, see *Warnings and Precaution*s.

**From spontaneous post-marketing reporting.

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

Description of selected adverse reaction

Local injection site reactions

In 2 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.

Paediatric population

Thirty-six children (aged 6-11) with severe eosinophilic asthma received *NUCALA* in an open-label study for 12 weeks. After a treatment interruption of 8 weeks, 30 of these patients received *NUCALA* for a further 52 weeks. No additional adverse reactions were identified compared to those reported for the adolescent and adult severe asthma studies.

Post-marketing data

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

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

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 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with *NUCALA*. The magnitude of reduction in the indicated populations described below were observed within 4 weeks of treatment and were maintained throughout the treatment period.

In patients with severe asthma (adults/adolescents), 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 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.

In children 6 to 11 years old with severe asthma, following either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 48 and 44 cells/µL, respectively with a reduction from baseline of 85% and 87%, respectively.

Immunogenicity

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

In adult/adolescent subjects who received at least one dose of mepolizumab administered subcutaneously every four weeks, 15/260 (6%) (100 mg, severe asthma), 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.

In children 6 to 11 years with severe asthma following either 40 mg SC (for a weight < 40kg) or 100 mg SC (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study.

Across indications neutralising antibodies were detected in one adult subject (with severe asthma). 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 titres and change in eosinophil level.

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. Subcutaneous administration of mepolizumab 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.

Children

Mepolizumab pharmacokinetics following subcutaneous administration in subjects 6 to 11 years old with severe asthma was investigated in an open label, uncontrolled study of 12-week duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg.

Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

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 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.

Clinical Studies

Severe 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)].

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 patients included in the Study MEA112997 and Study MEA115588 weigh ≥45kg. 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 FEV1<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 FEV1 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 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, results demonstrated that *NUCALA* significantly reduced 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).

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.

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 *NUCALA* as add-on therapy in 576 patients with severe 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.

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 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 endpoint and secondary endpoints of MEA115588.

Table 2: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

	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 (*NUCALA* 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 (*NUCALA* 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		

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
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 (MEA115575)

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. 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].

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 4).

Table 4: 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 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.

Paediatric population

There were 25 adolescents - 13 girls and 12 boys, 9 aged 12 -14 years and 16 aged 15-17 years enrolled in study MEA115588. Of the total 25 subjects: 9 received placebo, 9 received mepolizumab 75 mg intravenously, and 7 received 100 mg mepolizumab subcutaneously. The same proportion of subjects (3/9) receiving placebo and mepolizumab intravenously reported clinically significant exacerbations; no exacerbations were reported in those receiving mepolizumab subcutaneously.

Study 200363 was a multi-centre, open-label, uncontrolled, study that enrolled 36 children (6 to 11 years of age) with severe eosinophilic asthma. Subjects received 40 mg SC of Nucala (for a weight < 40 kg) or 100 mg SC of Nucala (for a weight ≥ 40 kg) every

4 weeks. The short-term phase (12 weeks) characterised the pharmacokinetics and pharmacodynamics of mepolizumab in children (see Pharmacokinetics and Pharmacodynamics). Following a treatment interruption of 8 weeks, the long-term phase (52 weeks) assessed safety and tolerability.

The efficacy of Nucala in children (6 to 11 years of age) for a 40 mg SC dose is extrapolated from efficacy in adults and adolescents with support from population pharmacokinetic analyses and pharmacodynamic analyses. The disease course, pathophysiology, and drug effects in children are assumed to be sufficiently consistent to adults and adolescents at the same exposure levels.

Non-Clinical Information

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

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.

The 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 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 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.

Incompatibilities

No incompatibilities have been identified.

Use and Handling

See the Instructions for Use leaflet for complete administration instructions with illustrations.

Product Registrant: GlaxoSmithKline Pte Ltd, 23 Rochester Park, Singapore 139234

Version number: GDS15/IPI01(SI)

Date of issue: 13 August 2021

[GSK logo]

PATIENT INFORMATION LEAFLET

NUCALA 40 mg in 0.4 mL pre-filled syringe (safety syringe).
Mepolizumab

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any questions, ask your doctor or nurse.

If you notice any side effects that bother you or do not go away, please tell your doctor or nurse.

In this leaflet

1. What NUCALA is and what it is used for

NUCALA contains the active substance **mepolizumab**, a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat severe asthma in children 6 to 11 years of age.

Mepolizumab, the active substance in NUCALA lowers the number of *eosinophils* **(a type of white blood cell)** in the bloodstream, lungs and tissues.

Severe Eosinophilic Asthma

Some people with severe asthma have too many *eosinophils* in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma NUCALA can treat.

If your asthma is not well controlled by your existing treatment, NUCALA can reduce your number of asthma attacks.

If you are taking medicines called *oral corticosteroids*, NUCALA can also help reduce the daily dose you need to control your asthma.

2. Before you are given NUCALA

You must not receive NUCALA

If you are allergic to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

➔ Check with your doctor if you think this applies to you.

Take special care with NUCALA

NUCALA should not be used to treat sudden breathing problems that may occur with asthma.

Some people get asthma related side effects, or their asthma may become worse, during treatment with NUCALA.

➔ Tell your doctor or nurse if your asthma remains uncontrolled, or gets worse, after you start NUCALA treatment.

Allergic and injection site reactions

Medicines of this type (*monoclonal antibodies*) can cause severe allergic reactions when injected into the body.

➔ **Tell your doctor before you are given NUCALA** if you may have had a similar reaction to any injection or medicine.

Parasitic infections

NUCALA may weaken your resistance to infections caused by parasites. If you have a parasitic infection, it should be treated before you start treatment with NUCALA.
If you live in a region where these infections are common or if you are travelling to such a region:

➔ **Check with your doctor if you think any of these may apply to you.**

Children

This medicine is not intended for use in children below the age of 6 years for the treatment of severe asthma.

Other medicines and NUCALA

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma

- ✘ Don't suddenly stop taking your medicines for your asthma, once you have started NUCALA. These medicines (especially ones called corticosteroids) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to NUCALA.

Pregnancy and breast-feeding

If you are pregnant, if you think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

It is not known whether the ingredients of NUCALA can pass into breast milk. If you are breast-feeding, you must check with your doctor before you use NUCALA.

Driving and using machines

The possible side effects of NUCALA are unlikely to affect your ability to drive or use machines.

3. How NUCALA is used

NUCALA must be given by a caregiver or a doctor/nurse.

NUCALA is given by injection under the skin (subcutaneous injection).

A doctor or nurse will decide if you can inject NUCALA to the child you are caring for. If appropriate, they will then provide training to show you the correct way to use NUCALA.

You can inject NUCALA under the skin in the stomach area (abdomen), in the upper leg (thigh) or in the upper arm of the child. You should not give injections into areas where the skin is tender, bruised, red or hard.

Children aged 6 to 11 years of age

The recommended dose is one 40 mg injection every four weeks.

If a dose of NUCALA is missed

If you forget to give the injection of NUCALA using a pre-filled syringe:

➔ You should inject the next dose of NUCALA as soon as you remember. If you do not notice that you have missed a dose until it is already time for the next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Don't stop NUCALA without advice

Do not stop injections of NUCALA unless your doctor advises you to. Interrupting or stopping the treatment with NUCALA may cause your symptoms to come back.

➔**If your symptoms get worse while receiving injections of NUCALA call your doctor.**

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by NUCALA are usually mild to moderate but can occasionally be serious.

Allergic reactions

Allergic reactions, which may be severe (e.g. anaphylaxis) to NUCALA are rare (they may affect up to 1 in 1000 people).
If you have any of the following symptoms after taking NUCALA:

- skin rash (hives) or redness
- swelling, sometimes of the face or mouth (angioedema)
- becoming very wheezy, coughing or having difficulty in breathing
- suddenly feeling weak or light headed (may lead to collapse or loss of consciousness)

➔Stop using NUCALA and seek medical help immediately

Very common side effects

These may affect **more than 1 in 10** people:

- headache

Common side effects

These may affect **up to 1 in 10** people:

- chest infection- symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare side effects

These may affect **up to 1 in 1,000** people:

- allergic reactions which may be severe (e.g. anaphylaxis) (See earlier in **Section 4***).*

➔ **Tell your doctor or pharmacist if any of the side effects listed becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.**

5. How to Store NUCALA

Keep this medicine out of the sight and reach of children.

Do not use NUCALA after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

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

Store in the original carton to protect from light.

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

The pre-filled syringe can be removed from the refrigerator and kept in its unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light.

6. Further information

What NUCALA contains

The active substance is mepolizumab.

Each 0.4 mL pre-filled syringe contains 40 mg mepolizumab

Other ingredients are:
Sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, EDTA disodium dehydrate and Water for Injection.

What NUCALA looks like and contents of the pack

NUCALA is supplied as a clear, colourless to pale yellow to pale brown solution in a 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 available in a pack containing 1 single-use pre-filled syringe.

[GSK logo]

INSTRUCTIONS FOR USE

NUCALA 40 mg/0.4 mL 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 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.
- Do not store it above 30°C.
- Safely throw it away if it has been removed from the refrigerator and not been used within 7 days.

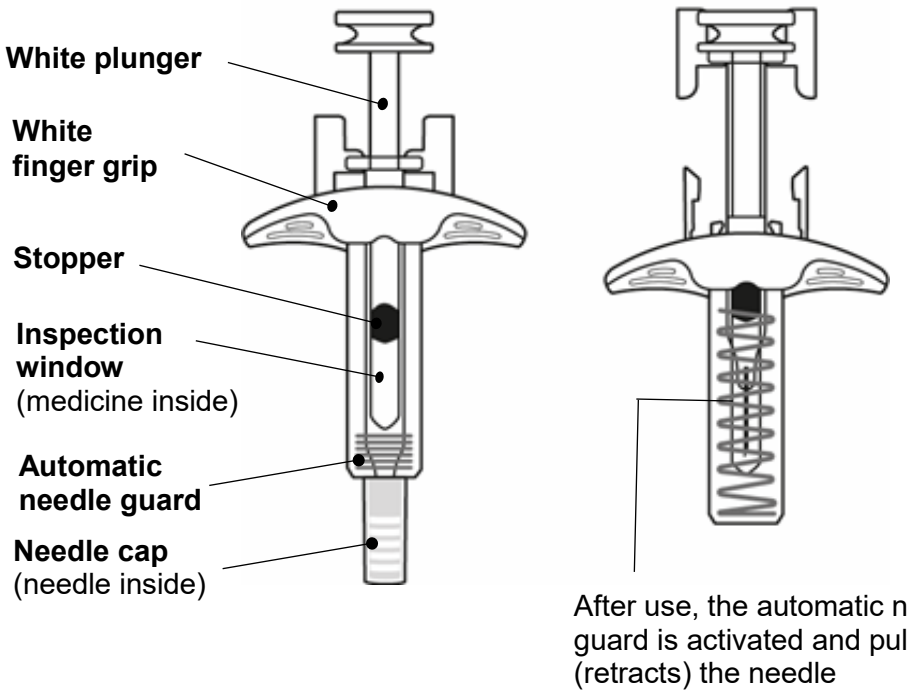
Before you use NUCALA

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

- **Do not** share the 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 the injection.

Know the prefilled syringe

Before Use **After Use**

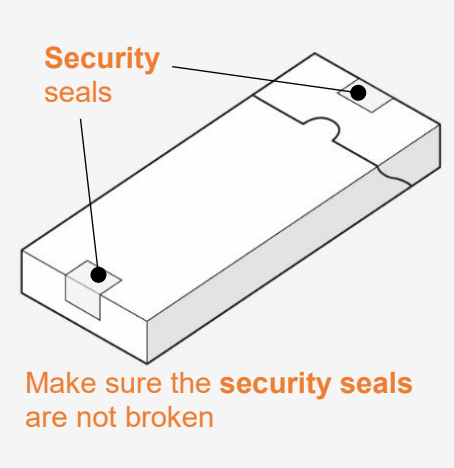


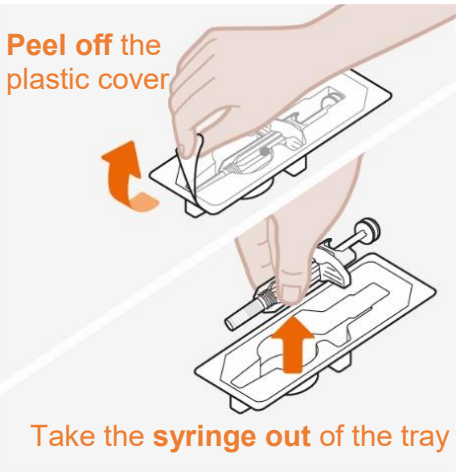
Prepare

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 the pre-filled syringe

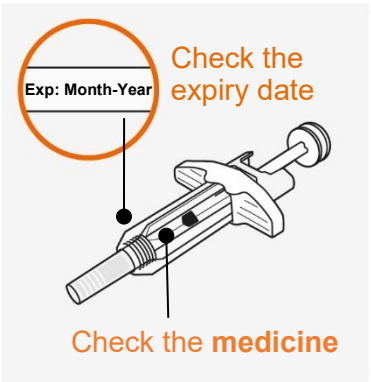


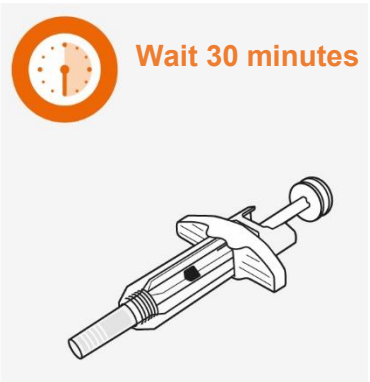


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away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

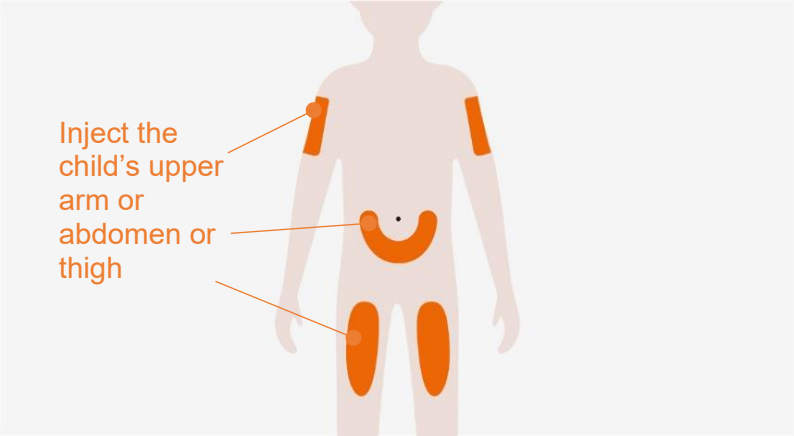




- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

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

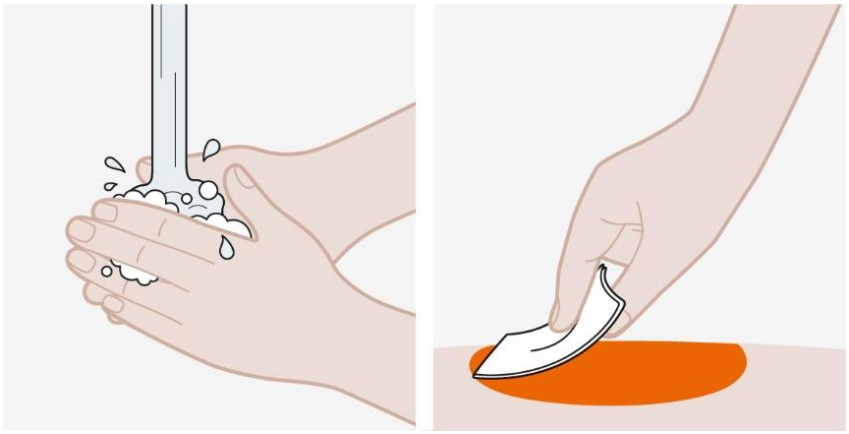
4. Choose the injection site



- You can inject NUCALA into the upper arm, abdomen or thigh of the child you are caring for.

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

5. Clean the injection site

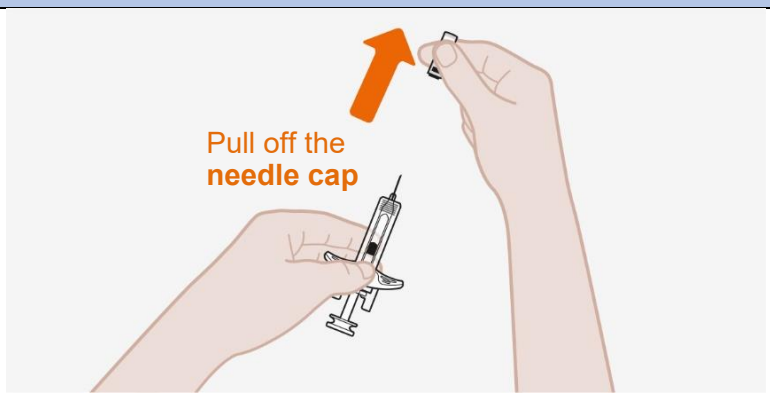


- Wash your hands with soap and water.
- Clean the injection site by wiping the skin with an alcohol swab and allowing the skin to air dry.

Do not touch the cleaned injection site again until you have finished the 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.

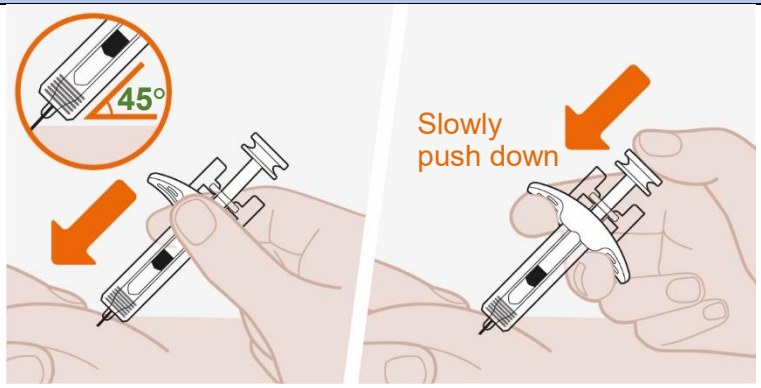
Do not touch the needle.

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

Do not expel any air bubbles from the syringe.

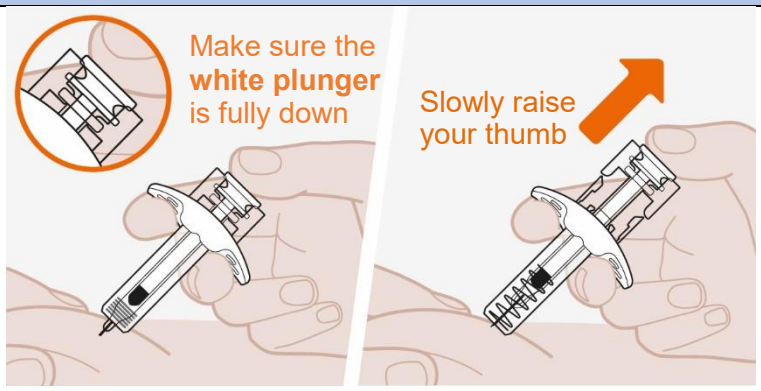
Do not put the needle cap back onto the syringe. This could cause a needle injury.

7. Start the injection



- Use your free hand to pinch the skin around the injection site. Keep the skin pinched throughout the 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 the full dose.

8. Complete the 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 the 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 the used syringes and needle caps out of the sight and reach of children.