ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXDENSUR 100 mg solution for injection in pre-filled pen
EXDENSUR 100 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 100 mg of depemokimab.

Depemokimab is a recombinant humanised (IgG1, kappa) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

Each mL of solution for injection contains 0.2 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless, yellow to brown, clear to opalescent solution, with a pH of 6.0 and an osmolality of 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

EXDENSUR is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

4.2 Posology and method of administration

This medicinal product should be prescribed by physicians experienced in the diagnosis and treatment of asthma or CRSwNP.

Posology

This medicinal product is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on the patient's level of disease control.

Asthma

Adults and adolescents aged 12 years and over

The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months.

CRSwNP

Adults

The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months.

Missed dose

If a dose is missed, it should be administered as soon as possible. If the missed dose is taken 1 month or longer after the scheduled dose, the 6-monthly injection schedule should be resumed from the date when the missed dose was given.

Special populations

Elderly

No dose adjustment is required for elderly patients aged ≥ 65 years old (see section 5.2).

Renal or hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Asthma

The safety and efficacy of depemokimab in children aged less than 12 years have not yet been established. No data are available.

CRSwNP

There is no relevant use of depemokimab in the paediatric population for the treatment of CRSwNP.

Method of administration

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

This product may be self-administered by adult or adolescent patients 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, except for the 5 cm around the navel. A caregiver can also inject the solution into the upper arm. It should not be injected into areas where the skin is bruised, tender, erythematous, or hardened.

Comprehensive instructions for administration are provided in the instructions for use at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions, such as anaphylaxis and angioedema, may occur following administration of depemokimab (see section 4.8). These reactions may occur within hours of administration, but some may have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated, is recommended. Upon re-administration of depemokimab monitoring to detect signs of recurring hypersensitivity reactions is recommended. In case of a severe or recurring hypersensitivity reaction, permanent discontinuation of depemokimab should be considered.

Acute asthma exacerbations

Depemokimab must not be used to treat acute asthma symptoms or acute exacerbations.

Asthma-related adverse symptoms or exacerbations may occur during treatment with depemokimab. It is recommended that patients be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with depemokimab.

Corticosteroids

Abrupt discontinuation of background treatments (including systemic and inhaled corticosteroids) after initiation of depemokimab therapy is not recommended. Reductions in the doses of background treatments, if appropriate, must be gradual and performed under the supervision of a physician.

Parasitic (helminth) infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from the clinical programme. Patients with pre-existing helminth infections should be treated for their infection prior to depemokimab therapy. If patients become infected while receiving treatment with depemokimab and do not respond to anti-helminth treatment, delaying administration of the next depemokimab dose until the infection resolves should be considered.

Excipients with known effect

Polysorbates
This medicinal product contains 0.2 mg of polysorbate 80 per 100 mg dose (see section 2). Polysorbates may cause allergic reactions.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The potential for drug-drug interactions is considered to be low as depemokimab is catabolised by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. The risk of drug disease interaction due to an indirect effect on gene expression of cytochrome P450 (CYP450) or transporters is also considered to be low since the specific target for depemokimab is the cytokine interleukin-5 (IL-5).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of depemokimab in pregnant women. Animal studies targeting IL-5 signalling pathways do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Monoclonal antibodies, such as depemokimab, are expected to be transported across the placenta in a linear fashion as pregnancy progresses.

As a precautionary measure, it is preferable to avoid the use of EXDENSUR during pregnancy.

Breast-feeding

It is unknown whether depemokimab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, EXDENSUR could be used during breast-feeding if clinically needed.

Fertility

There are no fertility data in humans. Animal studies have shown no adverse effects of anti-IL-5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported with depemokimab are local injection site reactions (2%).

Tabulated list of adverse reactions

Adverse reactions reported during clinical trials are presented in the table below (Table 1).

Frequencies are defined as 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) and very rare (< 1/10 000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System Organ Class	Adverse reactions	Frequency
Skin and subcutaneous tissue disorders	Pruritus	Common
General disorders and administration site conditions	Administration-related systemic reactions (non-allergic)	Common
	Local injection site reactions	Common

Description of selected adverse reactions

Systemic reactions (allergic)

Hypersensitivity reactions, such as anaphylaxis and angioedema, have been reported with other monoclonal antibodies that target IL-5 or its receptor. These reactions may occur based on the experience with the class (see section 4.4).

Systemic reactions (non-allergic)

Administration-related non-allergic reactions (e.g., headache, fatigue, rash) were reported in 1% of patients receiving depemokimab in the entire clinical development programme. In the 52-week placebo-controlled studies in asthma and CRSwNP, systemic non-allergic reactions were reported in < 1% of patients receiving depemokimab.

Systemic reactions (non-allergic) reported with depemokimab were non-serious and were either mild or moderate in intensity. The majority of events were transient: 88% of events resolved ≤ 7 days from onset whereas, 67% of events resolved ≤ 2 days from their onset.

Local injection site reactions

Local injection site reactions (e.g., pain, erythema, swelling, itching) were reported in 2% of patients receiving depemokimab in the entire clinical development programme. The reactions reported with depemokimab were non-serious, mild in intensity and were transient (79% resolved in ≤ 7 days, with most events (56%) resolving in ≤ 2 days from their onset).

In the placebo-controlled studies in asthma and CRSwNP, local injection site reactions were reported in 1% of patients receiving depemokimab compared to < 1% of patients who received placebo.

Paediatric population

Fifteen adolescents (aged 12-17) received depemokimab in two placebo-controlled studies for asthma (SWIFT-1 and SWIFT-2) of 52 weeks duration. The safety profile was generally similar to that seen in adults. No additional adverse reactions were identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses of up to 300 mg have been administered subcutaneously without evidence of dose-related toxicities.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airways diseases, ATC code: R03DX12

Mechanism of action

Depemokimab targets human IL-5 with a binding affinity of 10.5 pM, thereby blocking the binding to the IL-5 receptor alpha expressed on the cell surface with picomolar potency (IC50 4 pM) *in vitro*. Depemokimab contains a triple amino acid substitution (YTE) in the fragment crystallisable (Fc) region which increases binding to the neonatal Fc receptor and thereby extends the half-life when compared to the IgG1 wildtype.

IL-5 is a pleiotropic cytokine with established impact on eosinophils and other immune and structural cells. In severe asthma, inhibition of IL-5 has demonstrated an improvement in epithelial integrity, mucus plugging and reduction in tissue remodelling. However, the mechanism of action has not been definitively established.

Pharmacodynamic effects

In a clinical pharmacology study with mild-to-moderate asthma patients, a single 100 mg subcutaneous dose of depemokimab produced a rapid reduction in blood eosinophil count. Blood eosinophils were reduced by 54% compared to placebo 24 hours after dosing, which was the first post-dose assessment.

In the asthma and CRSwNP phase 3 studies, these reductions were sustained over the treatment period and blood eosinophil count reductions at week 52 were 79% and 85% compared to placebo, respectively.

Immunogenicity

In patients who received at least one 100 mg dose of depemokimab administered subcutaneously every 6 months, 9% (44/499) of patients with asthma (SWIFT-1 and SWIFT-2) and 8% (21/272) of patients with CRSwNP (ANCHOR-1 and ANCHOR-2) were positive for anti-depemokimab antibodies (ADA) during the 52-week studies.

The percentage of patients who were positive for ADA was 9% (55/622) in a 52-week open-label extension asthma study (AGILE; n = 395 with data collected for 104 weeks).

Across the placebo-controlled studies for asthma and CRSwNP indications, and the 52-week open label extension asthma study (AGILE), < 1% of the patients (n = 7) were positive for neutralising antibodies.

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy or safety was observed; however, data are still limited.

Clinical efficacy and safety

Asthma

The efficacy of depemokimab was evaluated in 2 replicate, randomised (2:1 ratio, depemokimab to placebo), double-blind, placebo-controlled, parallel-group, multi-centre clinical studies of 52-weeks treatment duration (SWIFT-1 and SWIFT-2). The two studies enrolled patients aged 12 years and older with asthma with type 2 inflammation characterised by an eosinophilic phenotype. In these studies, depemokimab 100 mg was administered subcutaneously once every 6 months for a total of 2 doses in addition to standard of care (SoC) therapy. Patients were required to have 2 or more asthma exacerbations requiring treatment with systemic corticosteroids (SCS) in the last 12 months, while on medium- to high-dose ICS (≥ 440 mcg fluticasone propionate or equivalent) plus at least one additional asthma controller. Patients were also required to have a blood eosinophil count of ≥150 cells/mcL at screening or ≥300 cells/mcL documented in the year prior to study entry and reduced lung function at baseline (pre-bronchodilator forced expiratory volume in 1 second [FEV_1] < 80% predicted normal in adults and [FEV_1] < 90% or FEV_1:FVC ratio < 0.8 in adolescents). Patients were enrolled without requiring a minimum baseline Asthma Control Questionnaire-5 (ACQ-5) score. Depemokimab was administered as add-on to background asthma treatment which continued throughout the duration of the studies. The Full Analysis Set (FAS) population consisted of 762 patients who were randomised and received at least one dose of depemokimab or placebo in the two studies (382 in SWIFT-1 and 380 in SWIFT-2).

The demographics and baseline characteristics of the patients in these 2 studies are provided in Table 2.

Table 2. Demographics and baseline characteristics (FAS population)

	SWIFT-1 (N = 382)	**SWIFT-2 (N = 380)**
Age (y) of patients, mean (SD)	54 (14.2)	53 (16.2)
Patients aged ≥ 65 years, n (%)	98 (26)	96 (25)
Female, n (%)	223 (58)	241 (63)
White, n (%)	316 (83)	272 (72)
Duration of asthma, years, mean (SD)	22 (16.2)	25 (18.5)
Mean pre-bronchodilator % predicted FEV_1 (SD)	62 (15.2)	62 (15.9)
Mean % reversibility (SD)	17 (15.3)	18 (17.4)
Mean number of exacerbations in previous year (SD)	2.2 (0.69)	2.7 (1.92)
Eosinophil count, cells/mcL, median (min, max)	310 (20, 2 360)	340 (10, 4 440)
Total IgE, U/mcL, median (min, max)	185 (1.9, 12 142)	180 (2.2, 16 198)
Mean SGRQ total score (SD), range 0-100	44.3 (20.70)	44.5 (18.69)
Patients with ACQ ≥1.5 at baseline, n (%)	280 (75)	279 (75)
Medium-dose ICS use, n (%)[a]	179 (47)	154 (41)
High-dose ICS use, n (%)[a]	203 (53)	226 (59)
ICS + LAMA + LABA use, n (%)	95 (25)	127 (33)
Maintenance OCS use, n (%)	21 (5)	19 (5)

FAS = Full Analysis Set, FEV_1 = Forced Expiratory Volume in 1 second, IgE = immunoglobulin E, SGRQ = St. George's Respiratory Questionnaire, ACQ-5 = Asthma Control Questionnaire, ICS = inhaled corticosteroid, OCS = oral corticosteroid
[a] Medium-dose ICS = 440 mcg FP daily or equivalent; High-dose ICS > 440 mcg FP daily or equivalent

Exacerbations

The primary efficacy endpoint for SWIFT-1 and SWIFT-2 was the annualised rate of clinically significant exacerbations over the 52-week treatment period. A clinically significant exacerbation was defined as worsening of asthma requiring use of SCS (intravenous or oral steroids for at least 3 days or a single intramuscular corticosteroid dose) and/or hospitalisation and/or emergency department visit. For patients on maintenance SCS, at least double the existing maintenance dose for at least 3 days was required. All patients experiencing an exacerbation were treated with SCS. The majority of patients (95% and 92% for SWIFT-1 and SWIFT-2, respectively) completed the studies.

In SWIFT-1 and SWIFT-2, the annualised rate of asthma exacerbations was significantly lower in patients receiving depemokimab compared to placebo (Table 3). The percentage of patients with exacerbations requiring hospitalisation and/or emergency department visit was lower for patients treated with depemokimab (1% and 4%) compared with placebo (8% and 10%) in SWIFT-1 and SWIFT-2, respectively.

Table 3. Results of primary exacerbation endpoint (FAS population)

	SWIFT-1		**SWIFT-2**	
	Depemokimab N = 250	**Placebo N = 132**	**Depemokimab N = 252**	**Placebo N = 128**
Annualised asthma exacerbations rate				
Percent of patients with an exacerbation	32%	46%	32%	50%
Exacerbation rate per year	0.46	1.11	0.56	1.08
Rate ratio (95% CI) Percent reduction (95% CI)	0.42 (0.30, 0.59) 58% (41, 70)		0.52 (0.36, 0.73) 48% (27, 64)	
p-value	<0.001		<0.001	

FAS = Full Analysis Set

Secondary endpoints

Additional efficacy assessments included health-related quality of life measured with St. George's Respiratory Questionnaire (SGRQ), asthma control measured with Asthma Control Questionnaire (ACQ-5) and lung function (pre-bronchodilator FEV_1). Table 4 provides the results of these secondary endpoints for the FAS population of SWIFT-1 and SWIFT-2.

Table 4. Results of secondary endpoints (FAS population)

	SWIFT-1		**SWIFT-2**	
	Depemokimab N = 250	**Placebo N = 132**	**Depemokimab N = 252**	**Placebo N = 128**
St. George's Respiratory Questionnaire (SGRQ) total score at Week 52				
n[a]	224	114	224	116
LS mean change from baseline (SE)	-13.0 (1.11)	-9.7 (1.55)	-14.8 (1.04)	-12.5 (1.46)
Adjusted treatment difference[b]	-3.4		-2.3	
(95% CI)	(-7.1, 0.4)		(-5.8, 1.2)	

Asthma Control Questionnaire-5 (ACQ-5) score at Week 52				
n[a]	224	114	224	116
LS mean change from baseline (SE)	-0.82 (0.066)	-0.77 (0.091)	-0.81 (0.065)	-0.70 (0.091)
Adjusted treatment difference[b]	-0.04		-0.11	
(95% CI)	(-0.27, 0.18)		(-0.33, 0.11)	
Pre-bronchodilator FEV_1 (mL) at Week 52				
n[a]	224	115	226	112
LS mean change from baseline (SE)	160 (26.3)	160 (36.4)	240 (28.6)	184 (40.7)
Adjusted treatment difference[b]	-1		56	
(95% CI)	(-89, 88)		(-43, 154)	

FAS = Full Analysis Set, LS = Least Squares, FEV_1 = Forced Expiratory Volume in 1 second
[a] Number of patients with analysable data at the timepoint
[b] Adjusted treatment difference (depemokimab vs. placebo)

Open-label extension study in asthma (AGILE)

Patients who completed either the SWIFT-1 or SWIFT-2 study were able to enrol in an open-label extension study (AGILE) where they all received up to two doses of depemokimab over an additional 52 weeks. The analysis of AGILE (n = 629) showed an annualised exacerbation rate of 0.56 (95% CI: 0.49, 0.65).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

The efficacy of depemokimab in adult patients with CRSwNP was evaluated in 2 replicate, randomised, double-blind, placebo-controlled, parallel-group, multicentre clinical studies of 52-weeks duration (ANCHOR-1 and ANCHOR-2). These studies evaluated the efficacy of 100 mg of depemokimab administered subcutaneously once every 6 months for a total of 2 doses in addition to standard of care (SoC) therapy. Patients had been treated with systemic corticosteroids (SCS) anytime within the past 2 years; and/or had a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for nasal polyps (NP) prior to screening. Randomised patients were required to have an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 with a minimum score of 2 in each nasal cavity and a mean nasal obstruction Verbal Response Scale (VRS) score of 2 or greater at baseline. Other than nasal obstruction, there were no other entry requirements for symptoms or for quality of life at randomisation. A total of 528 patients (271 in ANCHOR-1 and 257 in ANCHOR-2) were included in the Full Analysis Set (FAS) population.

The demographics and baseline characteristics of the patients in these two studies are provided in Table 5 below:

Table 5. Demographics and baseline characteristics (FAS population)

	ANCHOR-1 N = 271	**ANCHOR-2 N = 257**
Age (y) of patients, mean (SD)	54 (13.4)	50 (12.9)
Patients aged ≥ 65 years, n (%)	57 (21)	43 (17)
Female, n (%)	83 (31)	80 (31)
White, n (%)	185 (70)	197 (77)
Duration (y) of CRSwNP, mean (SD)	13 (11.2)	11 (8.7)
Blood eosinophil count, cells/mcL, median (min, max)	360 (10, 10 550)	360 (30, 1 670)
Intranasal corticosteroid use, n (%)	265 (98)	249 (97)
Patients with ≥ 1 previous NP surgery, n (%)	171 (63)	162 (63)
SCS use for NP in past 12 months, n (%)	190 (70)	172 (67)

Medical contraindication/intolerance to SCS, n (%)	11 (4)	13 (5)
Asthma, n (%)	161 (59)	131 (51)
AERD, n (%)	43 (16)	42 (16)
Total endoscopic NP score[a b c], mean (SD), maximum score = 8	6.0 (1.35)	5.9 (1.29)
Nasal obstruction VRS mean score[a d], mean (SD), maximum score = 3	2.5 (0.48)	2.6 (0.42)
Loss of smell VRS mean score[a d], mean (SD), maximum score = 3	2.7 (0.55)	2.8 (0.41)
SNOT-22 total score[a e], mean (SD), maximum score = 110	57.4 (22.15)	60.1 (19.95)
Patients with SNOT-22 total score ≥ 40, n (%)	204 (75)	207 (81)

FAS = Full Analysis Set, CRSwNP = chronic rhinosinusitis with nasal polyps, SCS = systemic corticosteroid, NP = nasal polyp, AERD = aspirin-exacerbated respiratory disease, VRS = Verbal Response Scale, SNOT-22 = Sino-Nasal Outcome Test

[a] Higher scores indicate greater disease severity.

[b] As graded by independent blinded assessors.

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

[d] Collected daily by patients on a 0 to 3 scale where 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms.

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

Total endoscopic nasal polyp score and nasal obstruction VRS score

The co-primary efficacy endpoints in each study were change from baseline in total endoscopic NP score (0-8 scale) at Week 52 as graded by central blinded readers and change from baseline in mean nasal obstruction VRS score (0-3 scale [0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms]) over Weeks 49 to 52 as self-reported by patients using a daily diary. The results for the co-primary endpoints in the ANCHOR-1 and ANCHOR-2 studies are presented in Table 6.

Table 6. Results of co-primary endpoints (FAS population)

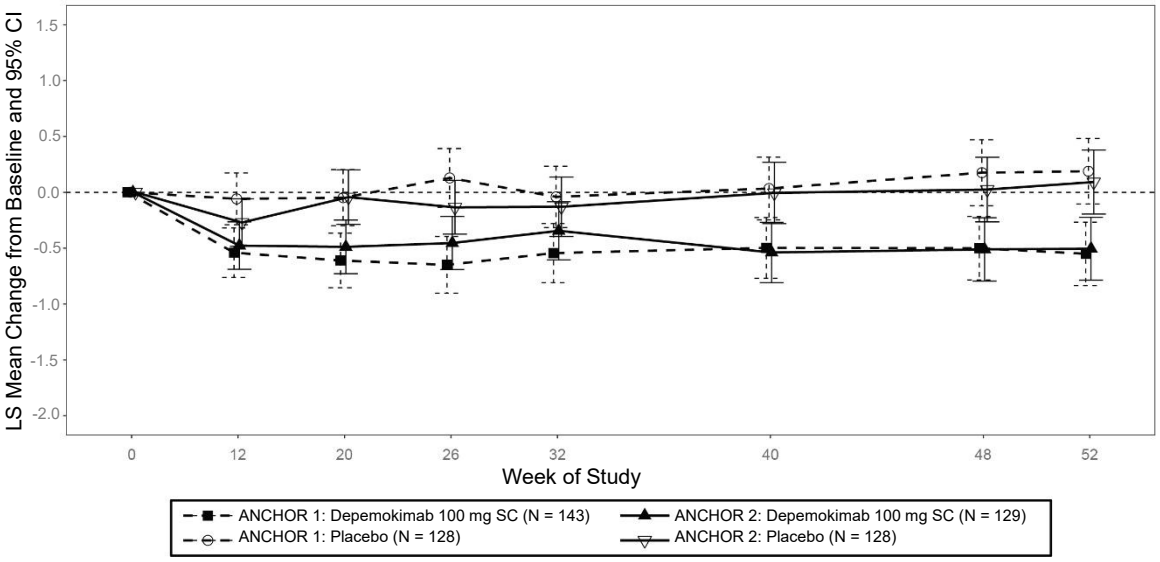
	ANCHOR-1		**ANCHOR-2**	
	Depemokimab N = 143	**Placebo N = 128**	**Depemokimab N = 129**	**Placebo N = 128**
Total endoscopic NP score at Week 52[a b]				
n[c]	128	120	120	115
LS mean (SE)	5.4 (0.14)	6.2 (0.15)	5.4 (0.14)	6.0 (0.15)
LS mean change from baseline (SE)	-0.6 (0.14)	0.2 (0.15)	-0.5 (0.14)	0.1 (0.15)
Adjusted treatment difference[d] (95% CI)	-0.7 (-1.1, -0.3)		-0.6 (-1.0, -0.2)	
p-value	<0.001		0.004	
Nasal obstruction VRS mean score over Weeks 49 to 52[a b]				
n[c]	125	116	119	111

LS mean (SE)	1.77 (0.079)	2.00 (0.083)	1.83 (0.076)	2.07 (0.078)
LS mean change from baseline (SE)	-0.76 (0.079)	-0.53 (0.083)	-0.77 (0.076)	-0.53 (0.078)
Adjusted treatment difference[d] (95% CI)	-0.23 (-0.46, 0.00[e])		-0.25 (-0.46, -0.03)	
p-value	0.047		0.025	

FAS = Full Analysis Set, NP = nasal polyp, LS = Least Squares, VRS = Verbal Response Scale
[a] Patients who had nasal surgery or used other maintenance treatment impacting type 2 inflammation (including biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids) prior to the timepoint of interest were assigned the worst possible value of the relevant score for all assessments following surgery or initiation of other maintenance treatment impacting type 2 inflammation.
[b] Based on Mixed Model Repeat Measures (MMRM) analyses with covariates of treatment, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline and visit by treatment.
[c] Number of patients with analysable data at the timepoint
[d] Adjusted treatment difference (depemokimab vs. placebo)
[e] The upper limit of the 95% CI represents a rounded number of -0.003.

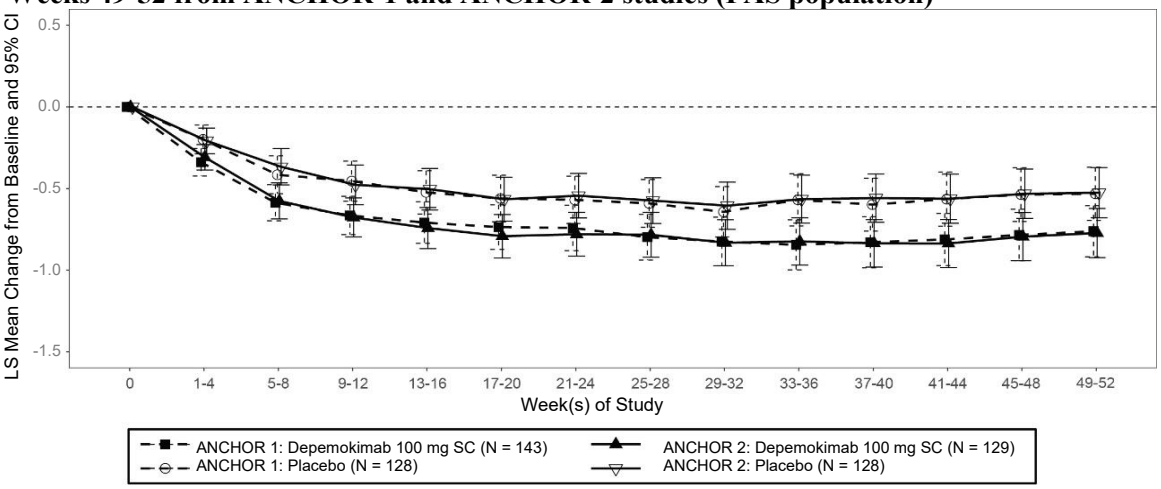
In analyses from the individual studies ANCHOR-1 and ANCHOR-2, a treatment difference in favour of depemokimab was observed by Week 12 (first timepoint assessed) for the total endoscopic NP score and by Weeks 1-4 (first timepoint assessed) for the nasal obstruction VRS mean score that was maintained up to Week 52 (Figures 1 and 2).

Figure 1. LS mean change from baseline (95% CI) in total endoscopic NP score up to Week 52 from ANCHOR-1 and ANCHOR-2 studies (FAS population)



LS = Least Squares; NP = nasal polyp; FAS = Full Analysis Set

Figure 2. LS mean change from baseline (95% CI) in nasal obstruction VRS mean score up to Weeks 49-52 from ANCHOR-1 and ANCHOR-2 studies (FAS population)

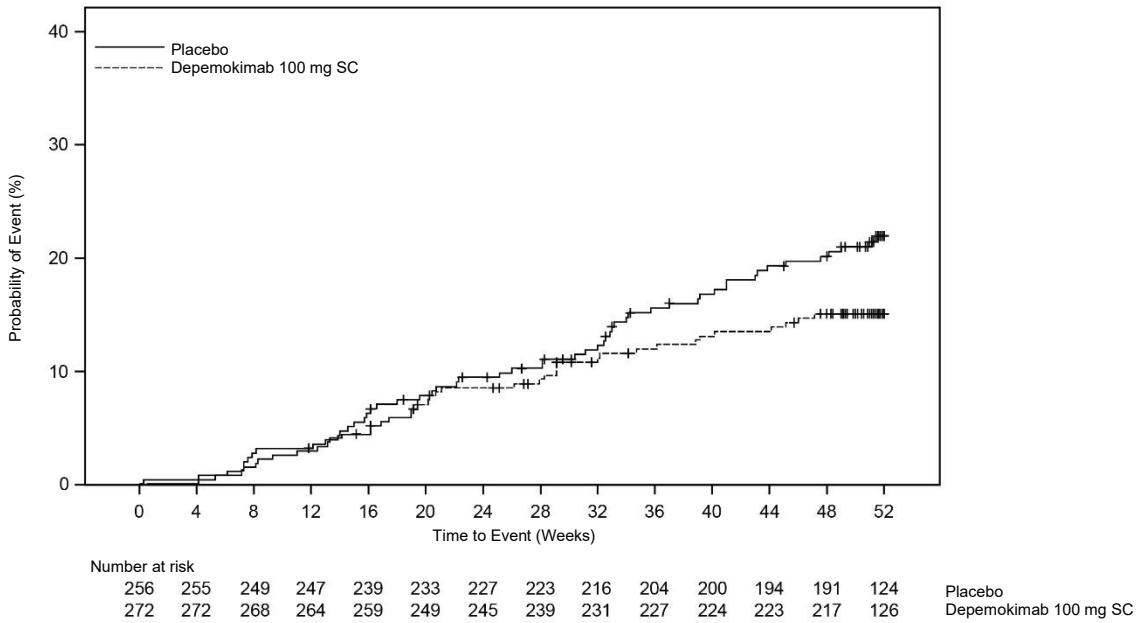


LS = Least Squares; VRS = Verbal Response Scale; FAS = Full Analysis Set

Nasal surgery, systemic corticosteroid use, initiation of other maintenance treatment impacting type 2 inflammation for CRSwNP

Across the two ANCHOR studies, the key secondary endpoint of the proportion of patients who required nasal surgery (actual or planned) or initiated other maintenance treatment impacting type 2 inflammation (including biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids) was 16% (44/272) in the depemokimab group and 22% (56/256) in the placebo group (27% risk reduction; HR: 0.735; 95% CI: 0.495, 1.092, Figure 3). The proportion of patients who had nasal surgery or initiated other maintenance treatment impacting type 2 inflammation for CRSwNP was 12% (33/272) in the depemokimab group, compared with 17% (43/256) in the placebo group, representing a 29% risk reduction (HR: 0.713; 95% CI: 0.453, 1.124).

Figure 3: Kaplan Meier curve for time to first nasal polyps surgery (actual or planned) or initiation of other maintenance treatment impacting type 2 inflammation[1] for CRSwNP up to Week 52 (pooled FAS population)



CRSwNP = chronic rhinosinusitis with nasal polyps; FAS = Full Analysis Set

[1]Other maintenance treatment impacting type 2 inflammation includes biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids.

Across the two ANCHOR studies, the proportion of patients that required at least 1 course of SCS for CRSwNP or other maintenance treatment impacting type 2 inflammation for CRSwNP or nasal surgery was 26% (72/272) in the depemokimab group compared with 36% (92/256) in the placebo group (OR: 0.58, 95% CI: 0.40, 0.86).

Paediatric population

Asthma

In the SWIFT-1 and SWIFT-2 studies, there were 30 adolescents (12 to 17 years old), of which 15 received placebo and 15 received depemokimab 100 mg subcutaneously. In a combined analysis of these studies, a 43% reduction in clinically significant exacerbations was observed in adolescents following depemokimab treatment compared to placebo (rate ratio 0.57; 95% CI: 0.15, 2.13).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

There are no clinical data available in children and adolescents aged less than 18 years old.

The European Medicines Agency has waived the obligation to submit the results of studies with EXDENSUR in all subsets of the paediatric population in asthma and CRSwNP (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Depemokimab exhibited approximately dose-proportional pharmacokinetics over a dose range of 10 to 300 mg in patients with asthma following subcutaneous administration. After subcutaneous administration of 100 mg depemokimab every 6 months, the average concentrations (%CV) at steady state were 5.9 mcg/mL (28%) and 5.2 mcg/mL (27%) in asthma and CRSwNP patients, respectively. The Week 26 trough concentrations were 1.2 mcg/mL (37%) and 1.0 mcg/mL (36%) in asthma and CRSwNP patients, respectively.

Absorption

Following a single subcutaneous administration (doses ranging from 2 to 300 mg), maximum observed plasma concentrations (C_{max}) were achieved at a median time ranging from 8 to 14 days. After a single subcutaneous administration of 100 mg depemokimab, the average C_{max} (%CV) was 12.2 mcg/mL (16%).
Following two repeat subcutaneous administrations once every 6 months, achieving steady-state conditions, the depemokimab accumulation was negligible (< 10%).

Distribution

Following a single subcutaneous administration of depemokimab, the mean apparent volume of distribution is 6 to 9 L.

Biotransformation

Depemokimab is a monoclonal antibody which is catabolised by ubiquitous proteolytic enzymes not restricted to hepatic tissue.

Elimination

Following a single subcutaneous administration of depemokimab, the geometric mean terminal half-life ranged from 38 to 53 days, with geometric mean apparent clearance values ranging from 0.081 to 0.16 L/day.

Special populations

Body weight

Population pharmacokinetic analyses indicated that exposure to depemokimab decreases with increasing body weight. Weight was the major determinant of depemokimab exposure, and satisfied conventional allometry with coefficients of 0.841 for CL/F and 0.887 for V/F, typical for a mAb such as depemokimab. Over the body weight range of 54 to 108 kg (corresponding to the 5th to 95th percentiles), the difference in all exposure metrics was less than 1.3-fold. Thus, the magnitude of effect of body weight on depemokimab exposure is not considered clinically relevant within this body weight range. At high body weights (140-160 kg) the exposure may be decreased 2-fold. For such patients, reduced efficacy cannot be excluded.

Gender, ethnicity

Population pharmacokinetic analyses indicated there was no clinically relevant effect of gender or race on depemokimab pharmacokinetics.

Elderly

Available pharmacokinetic data in elderly patients (≥ 65 years old, N = 176) across all clinical studies showed that depemokimab pharmacokinetics were similar between adult patients and patients aged 65 years and older (up to 93 years), based on the population pharmacokinetic analysis.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of depemokimab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with impaired renal function. Data are limited (n = 2) in patients with an eGFR < 30 mL/min/1.73m^2, but CL/F values of these two patients fell within the range of patients with normal renal function.

Renal impairment is not expected to have a significant impact on clearance as depemokimab is not cleared renally.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of depemokimab. Since depemokimab 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 depemokimab. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) had no clinically relevant effect on depemokimab apparent clearance.

Paediatric population

Asthma

There are limited pharmacokinetic data available in the paediatric population (15 adolescent patients with asthma). The pharmacokinetics of depemokimab in adolescents aged 12 to 17 years were similar to adults (see section 4.2) and key pharmacokinetics parameters are presented in Table 7.

Table 7. Derived secondary pharmacokinetics parameters in patients who received depemokimab 100 mg subcutaneously every 26 weeks in the pooled SWIFT-1 and SWIFT-2 studies

Parameter - geometric mean (%CV)	Adolescents N = 15	Adults N = 479	Overall N = 494
$AUC_{tau, ss}$ (mcg*day/mL)	1051 (31)	1082 (28)	1081 (28)
$C_{av, ss}$ (mcg /mL)	5.8 (31)	5.9 (28)	5.9 (28)
$C_{max, 26-52}$ (mcg/mL)	14.6 (30)	13.6 (28)	13.6 (28)
$T_{max, 26-52}$ (day)	10.8 (9)	13.7 (18)	13.6 (18)
$C_{trough, week52}$ (mcg/mL)	1.1 (39)	1.3 (38)	1.3 (38)
$t_{1/2}$ (days)	44.7 (9)	48.7 (10)	48.6 (10)

$AUC_{tau,ss}$; area under the concentration-time curve during a dosing interval at steady state, $C_{av,ss}$; average concentration during a dosing interval, $C_{max, 26-52}$; maximum concentration during the second dosing interval, $T_{max, 26-52}$; time to maximum concentration during the second dosing interval, $C_{trough, week 52}$; trough concentration at the end of the second administration, $t_{1/2}$; half-life

The pharmacokinetics of depemokimab have not been established in paediatric patients with asthma aged less than 12 years of age.

Pharmacokinetic/pharmacodynamic relationship

There is a clear relationship between depemokimab pharmacokinetics and reduction in blood eosinophil counts (pharmacodynamics) with maximum achievable reduction of around 85% and a half-maximal effective concentration (EC_{50}) of 0.19 mcg/mL. The concentration associated with 90% of maximal effect (EC_{90}) was 0.75 mcg/mL.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity with safety pharmacology endpoints.

No genotoxicity, carcinogenicity or reproductive toxicology studies have been conducted with depemokimab.

In animal studies targeting IL-5 signaling pathways (e.g. knockout animal data and class effects), there were no developmental effects observed.

Male and female fertility are unlikely to be affected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys at exposures sufficiently in excess of the maximum human exposure. Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride
Trehalose dihydrate
Arginine hydrochloride
Disodium edetate
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

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

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

6.5 Nature and contents of container

EXDENSUR 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 size:
1 pre-filled pen

EXDENSUR 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 size:
1 pre-filled syringe

6.6 Special precautions for disposal and other handling

Before administration, the solution must be inspected visually. If the solution is cloudy, discoloured or contains particles, the solution must not be used.

After removing the pre-filled pen or pre-filled syringe from the refrigerator, the pen or syringe should be allowed to reach room temperature for at least 30 minutes before injecting the solution.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus

Dublin 24
D24 YK11
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EXDENSUR 100 mg solution for injection in pre-filled pen

EU/1/25/2007/001

EXDENSUR 100 mg solution for injection in pre-filled syringe

EU/1/25/2007/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GlaxoSmithKline LLC
893 River Road
Building 40
Conshohocken
Pennsylvania (PA) 19428
United States

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.p.A.,
Strada Provinciale Asolana N. 90,
43056 Torrile,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

EXDENSUR 100 mg solution for injection in pre-filled pen
depemokimab

2. STATEMENT OF ACTIVE SUBSTANCE

1 mL of solution contains 100 mg depemokimab.

3. LIST OF EXCIPIENTS

Also contains: histidine, histidine monohydrochloride, trehalose dihydrate, arginine hydrochloride, disodium edetate, polysorbate 80 (E 433), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen

1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use.
For single use only.
Read the package leaflet before use.
Do not use if the security seal on the carton is broken.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Do not shake.
Store in the original carton in order to protect from light.
Time out of refrigeration must not exceed a maximum of 7 days when protected from light and stored below 30°C. Discard if left out of the refrigerator for more than 7 days.
The pre-filled pen must be administered within 8 hours once removed from the carton. Discard if not administered within 8 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12 Riverwalk
Citywest Business Campus
Dublin 24
D24 YK11
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2007/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

exdensur pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

EXDENSUR 100 mg injection
depemokimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

EXDENSUR 100 mg solution for injection in pre-filled syringe
depemokimab

2. STATEMENT OF ACTIVE SUBSTANCE

1 mL of solution contains 100 mg depemokimab.

3. LIST OF EXCIPIENTS

Also contains: histidine, histidine monohydrochloride, trehalose dihydrate, arginine hydrochloride, disodium edetate, polysorbate 80 (E 433), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use.
For single use only.
Read the package leaflet before use.
Do not use if the security seal on the carton is broken.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Do not shake.
Store in the original carton in order to protect from light.
Time out of refrigeration must not exceed a maximum of 7 days when protected from light and stored below 30°C. Discard if left out of the refrigerator for more than 7 days.
The pre-filled syringe must be administered within 8 hours once removed from the carton. Discard if not administered within 8 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2007/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

exdensur syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

EXDENSUR 100 mg injection
depemokimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EXDENSUR 100 mg solution for injection in pre-filled pen
depemokimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EXDENSUR is and what it is used for
2. What you need to know before you use EXDENSUR
3. How to use EXDENSUR
4. Possible side effects
5. How to store EXDENSUR
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What EXDENSUR is and what it is used for

EXDENSUR contains the active substance depemokimab, a monoclonal antibody (a type of protein designed to recognise and attach to a specific target in the body).

EXDENSUR is used with other asthma medicines for the maintenance treatment of severe asthma in adults and adolescents aged 12 years and older. It is used in patients whose asthma is not properly controlled by high-dose inhaled corticosteroids plus another medicine to control asthma, and who have a type of airway inflammation called type 2 inflammation.

EXDENSUR is also used with other medicines to treat chronic rhinosinusitis with nasal polyps (CRSwNP) in adults. CRSwNP is a long-term inflammation of the nose and sinuses, where soft, painless growths called polyps block the airways and make breathing difficult.

Patients with some types of asthma and CRSwNP have high levels of a protein called interleukin-5 (IL-5), which plays a role in the immune system (the body's natural defences). IL-5 helps make and activate eosinophils, a type of white blood cell that can cause inflammation. The active substance in EXDENSUR, depemokimab, blocks IL-5. This reduces the number of eosinophils in the body, which helps to ease inflammation and improve symptoms of the disease.

2. What you need to know before you use EXDENSUR

Do not use EXDENSUR:
- if you are **allergic** to depemokimab or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening of asthma
EXDENSUR is not a rescue medicine and must 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 EXDENSUR.

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

Allergic reactions
Medicines of this type (monoclonal antibodies) can cause severe allergic reactions such as anaphylaxis and angioedema (rash, swelling of the face, throat or mouth, fast heartbeat, sweating, difficulty in breathing, collapse or loss of consciousness) (see section 4, 'Possible side effects'). These reactions may occur within hours after EXDENSUR is given, but in some cases they may occur days later.

➔ **Seek medical attention immediately** if you think you may be having a reaction.

If you may have had a similar reaction to any injection or medicine:

➔ **tell your doctor** before you are given EXDENSUR.

Parasitic infections
EXDENSUR may weaken your resistance to infections caused by parasites. If you have a parasitic infection, it should be treated before you start treatment with EXDENSUR. 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 and adolescents
This medicine is not intended for use in **children below 12 years of age** for the treatment of asthma, or in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

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

Other medicines for asthma or CRSwNP
× **Don't suddenly stop** taking your medicines for your asthma or CRSwNP once you have started EXDENSUR. These medicines (especially ones called corticosteroids) must be stopped gradually, under the direct supervision of your doctor.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, 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 EXDENSUR can pass into breast milk. If you are breast-feeding, you must check with your doctor before you use EXDENSUR.

Driving and using machines
EXDENSUR is unlikely to affect your ability to drive or use machines.

EXDENSUR contains polysorbates
This medicine contains 0.2 mg of polysorbate 80 per 100 mg dose. Polysorbates may cause allergic reactions. **Tell your doctor** if you have any known allergies.

EXDENSUR contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially "sodium-free".

3. How to use EXDENSUR

EXDENSUR is given by injection under the skin (*subcutaneous*).

The recommended dose

- **Asthma** — for adults and adolescents aged 12 years and older, the recommended dose is 100 mg. You will have **1 injection every 6 months**.

- **CRSwNP** — for adults, the recommended dose is 100 mg. You will have **1 injection every 6 months**.

How to use
Instructions for using the pre-filled pen are given on the reverse of this leaflet.

Your doctor or nurse will decide if you or your caregiver can inject EXDENSUR. If appropriate, they will then give you or your caregiver training to show you the correct way to use EXDENSUR.

You can inject EXDENSUR under your skin in your stomach area (abdomen) or upper leg (thigh). Your caregiver can also inject EXDENSUR into your upper arm. Do not inject into areas where the skin is tender, bruised, red, or hard.

➔ Contact your doctor or nurse if you find it difficult to inject yourself, or if you have any concerns about whether you have injected correctly or given yourself a complete dose.

If you forget to use EXDENSUR
If your doctor or healthcare professional usually gives you your injection of EXDENSUR:
➔ contact your doctor or hospital as soon as possible to re-schedule your appointment.
If you or your caregiver usually give the injection of EXDENSUR, and you miss a dose:
➔ inject a dose of EXDENSUR as soon as possible. After that, continue EXDENSUR on your usual planned injection day.

If you miss a dose by 1 month or more:
➔ inject a dose of EXDENSUR then restart your 6-month injection schedule from the day you inject the missed dose.
If you are not sure what to do, ask your doctor, pharmacist or nurse.

Don't stop EXDENSUR without advice
Do not stop injections of EXDENSUR unless your doctor advises you to. Interrupting or stopping the treatment with EXDENSUR may cause your symptoms to come back.
If your symptoms get worse while receiving injections of EXDENSUR:
➔ 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.

Common (may affect **up to 1 in 10** people):
- itching (pruritus)

- headache, tiredness, or rash around the time of injection
- reactions at the site of the injection such as pain, redness, swelling or itching

Side effects that have been seen with similar medicines:
- severe allergic reactions such as anaphylaxis and angioedema (rash, swelling of the face, throat or mouth, fast heartbeat, sweating, difficulty in breathing, collapse or loss of consciousness).

➔ **Seek medical attention immediately** if you think you may be having a reaction.

➔ **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.**

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EXDENSUR

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

Do not use this medicine 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 a refrigerator (2°C - 8°C).

Do not freeze.

Do not shake.

Store in the original carton in order to protect from light.

The pre-filled pen 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. After 7 days out of the refrigerator, dispose of the pen according to local health and safety laws.

The pre-filled pen must be used within 8 hours once the carton is opened. Discard if not used within 8 hours.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXDENSUR contains
- The active substance is depemokimab. Each mL of solution contains 100 mg of depemokimab.
- The other ingredients are histidine, histidine monohydrochloride, trehalose dihydrate, arginine hydrochloride, disodium edetate, polysorbate 80 (E 433), water for injections.

What EXDENSUR looks like and contents of the pack

EXDENSUR is supplied as a 1 mL colourless, yellow to brown, clear to opalescent solution in a single-use pre-filled pen.

EXDENSUR is available in packs containing 1 pre-filled pen.

Marketing Authorisation Holder
GlaxoSmithKline Trading Services Limited
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Citywest Business Campus
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D24 YK11
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.p.A.,
Strada Provinciale Asolana N. 90,
43056 Torrile,
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu

7. Step by step instructions for use

EXDENSUR 100 mg solution for injection in pre-filled pen
depemokimab
for subcutaneous use

This Instructions for Use contains information on how to inject EXDENSUR.

Read these sections first

Before using your EXDENSUR pre-filled pen, it is important that your healthcare provider explains your EXDENSUR dosing instructions, and shows you (or your caregiver) how to use the pen correctly.

Important information

Read all of these instructions before using your pen. If you do not follow these instructions, you may not get all your medicine.

Do not use EXDENSUR pen:

- if it has been frozen
- if it has been dropped or damaged
- if the security seal on the carton has been broken
- if the expiry date (EXP) has passed

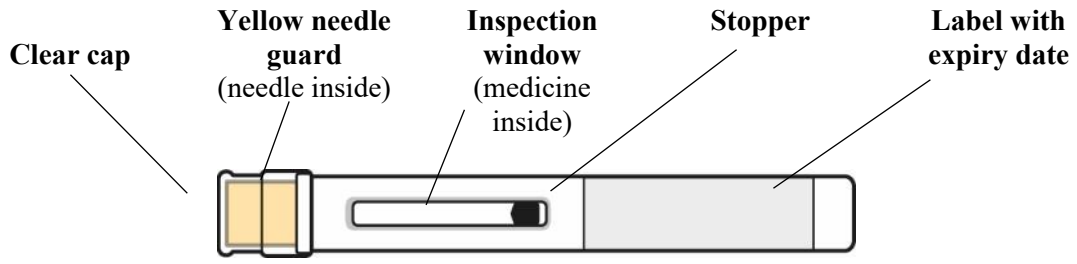
Do not:

- shake your EXDENSUR pen
- share your pen
- reuse your pen
- expose your pen to heat

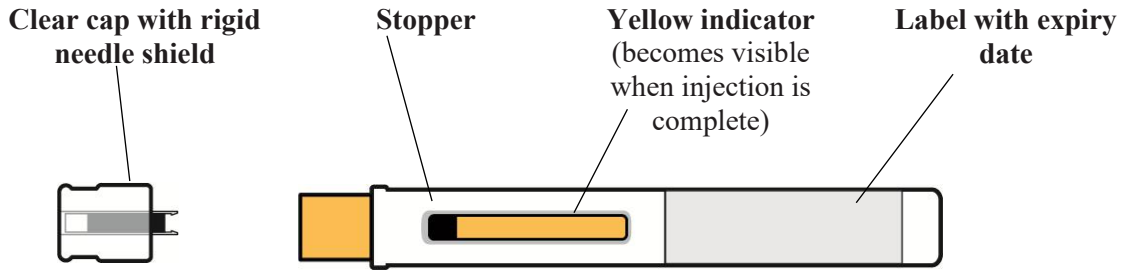
If any of these happen, dispose of the EXDENSUR pen according to local health and safety laws and use a new EXDENSUR pen. **Keep out of the sight and reach of children. Contains small parts.**

Get to know your EXDENSUR pre-filled pen

Before use



After use



Storage

Store the pen in its carton
Store EXDENSUR in a refrigerator (2°C - 8°C) in the original carton until you are ready to use it. **Do not** freeze.

An unopened carton of EXDENSUR pen may be kept at room temperature up to 30°C for a maximum of 7 days. After being brought to room temperature, EXDENSUR must be used within 7 days. After 7 days, dispose of the pen according to local health and safety laws.

Once the pen is removed from its carton
After the EXDENSUR pen is out of the carton, it must be used within 8 hours or dispose of the pen according to local health and safety laws. **Do not** place it back in the refrigerator.

A. Prepare

A1

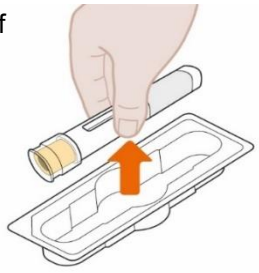
Gather supplies

Supplied
- EXDENSUR pen

Not supplied
- Alcohol swab
- Cotton ball or gauze
- Adhesive plaster
- Sharps disposal container (see Section C for disposal instructions).

A2

Take the **pre-filled pen out** of the tray



Take the carton containing your pen out of the refrigerator

- Holding the middle of the pen (near the inspection window), carefully take the pen out of the tray.
- **Do not** remove the clear needle cap at this step.

A3

Check the **expiry date** and the **medicine**

Check your pre-filled pen

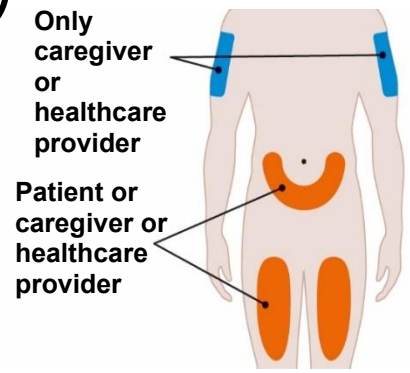
- Check the expiry date. **Do not** use if the expiry date has passed.
- Look at the medicine in the pre-filled pen through the inspection window. The medicine should be clear and colourless to yellow to brown.
- **Do not** inject if the medicine is cloudy, discoloured, or has particles.
- It is normal to see air bubbles. You **do not** need to do anything about it.
- **Do not** shake the pen.

A4

Wait 30 minutes

- **Do not** remove the clear cap.
- Place the pen on a clean, flat surface away from direct sunlight and out of the reach of children.
- **Wait 30 minutes** to bring to room temperature before you inject. Cold medicine is more painful to inject.
- **Do not** warm the pen in a microwave, hot water, or direct sunlight.
- **Do not** use the pen if it has been left out of the carton for more than 8 hours.

A5



Choose your injection site

- If you are giving yourself the injection, you can inject into your thighs or stomach (abdomen).
- A caregiver or healthcare provider can inject into the upper arm, thigh, or abdomen.
- **Do not** inject yourself in the upper arm, as it is more difficult to avoid pen movement during the injection.
- **Do not** inject where the skin is bruised, tender, red, or hard.
- **Do not** inject within 5 cm of your navel (belly button).

A6

Clean the injection site

- Wash your hands with soap and water.
- Clean the injection site with an alcohol swab. Allow skin to air dry.
- **Do not** fan or blow on the cleaned injection site.
- **Do not** touch the cleaned injection site again until you have finished your injection.

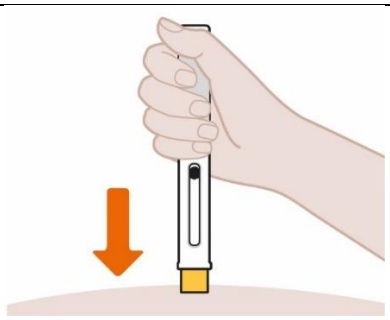
B. Inject

B1

Pull off the clear cap

- Remove the clear cap by pulling it straight off, away from the yellow needle guard. It may take some force to remove the clear cap.
- **Do not** press the yellow needle guard.
- **Do not** put the cap back on the pen. This could accidentally start the injection.
- You may see a drop of medicine at the end of the needle. This is normal.
- Inject within 5 minutes after you remove the clear cap.

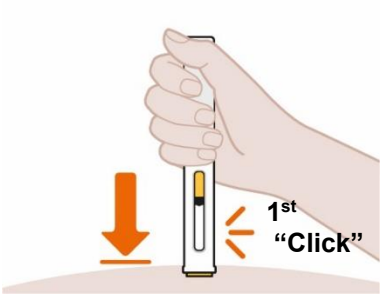
B2



Position the pen at the injection site

- Place the yellow needle guard flat against your skin.
- Make sure you can see the inspection window.

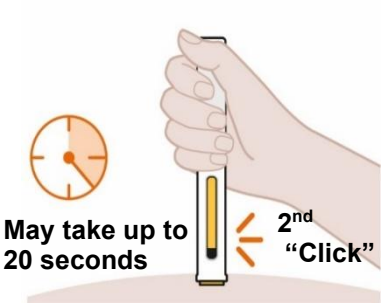
B3



Press firmly to start the injection

- The yellow needle guard will slide up into the pen.
- You may hear a "click" that tells you the injection has started.
- Keep the pen held down against the skin. **Do not** lift or move the pen during the injection.
- The yellow indicator will move down through the inspection window during the injection.
- **Do not** use the pen if the yellow needle guard does not slide up into the pen. Throw away the pen and clear cap according to local health and safety laws.

B4



Continue to hold down

Your injection is done when you hear the second "click". Injection may take up to 20 seconds.

If you do not hear the second "click", check that:

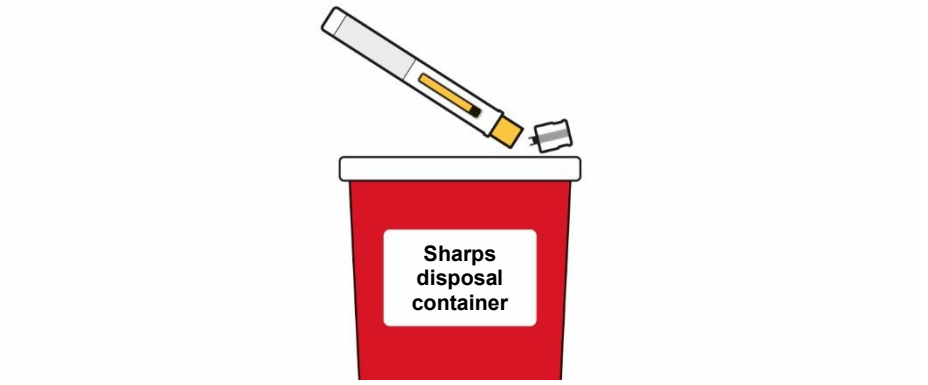
- the inspection window is filled with the yellow indicator.
- the black stopper has stopped moving.

B5

Lift the pen after the injection is complete

- **Do not** rub the injection site.
- **Do not** put the clear cap back onto the pen.
- There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive plaster if you need it.

C. Throw away



Dispose of your used pen and clear cap, according to local health and safety laws. Ask your doctor or pharmacist for advice if necessary.

Keep your used pens and needle caps out of the sight and reach of children.

Package leaflet: Information for the user

EXDENSUR 100 mg solution for injection in pre-filled syringe
depemokimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EXDENSUR is and what it is used for
2. What you need to know before you use EXDENSUR
3. How to use EXDENSUR
4. Possible side effects
5. How to store EXDENSUR
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What EXDENSUR is and what it is used for

EXDENSUR contains the active substance depemokimab, a monoclonal antibody (a type of protein designed to recognise and attach to a specific target in the body).

EXDENSUR is used with other asthma medicines for the maintenance treatment of severe asthma in adults and adolescents aged 12 years and older. It is used in patients whose asthma is not properly controlled by high-dose inhaled corticosteroids plus another medicine to control asthma, and who have a type of airway inflammation called type 2 inflammation.

EXDENSUR is also used with other medicines to treat chronic rhinosinusitis with nasal polyps (CRSwNP) in adults. CRSwNP is a long-term inflammation of the nose and sinuses, where soft, painless growths called polyps block the airways and make breathing difficult.

Patients with some types of asthma and CRSwNP have high levels of a protein called interleukin-5 (IL-5), which plays a role in the immune system (the body's natural defences). IL-5 helps make and activate eosinophils, a type of white blood cell that can cause inflammation. The active substance in EXDENSUR, depemokimab, blocks IL-5. This reduces the number of eosinophils in the body, which helps to ease inflammation and improve symptoms of the disease.

2. What you need to know before you use EXDENSUR

Do not use EXDENSUR:
- if you are **allergic** to depemokimab or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening of asthma
EXDENSUR is not a rescue medicine and must 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 EXDENSUR.

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

Allergic reactions
Medicines of this type (monoclonal antibodies) can cause severe allergic reactions such as anaphylaxis and angioedema (rash, swelling of the face, throat or mouth, fast heartbeat, sweating, difficulty in breathing, collapse or loss of consciousness) (see section 4, 'Possible side effects'). These reactions may occur within hours after EXDENSUR is given, but in some cases they may occur days later.

➔ **Seek medical attention immediately** if you think you may be having a reaction.

If you may have had a similar reaction to any injection or medicine:

➔ **tell your doctor** before you are given EXDENSUR.

Parasitic infections
EXDENSUR may weaken your resistance to infections caused by parasites. If you have a parasitic infection; it should be treated before you start treatment with EXDENSUR. 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 and adolescents
This medicine is not intended for use in **children below 12 years of age** for the treatment of asthma, or in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

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

Other medicines for asthma or CRSwNP
× **Don't suddenly stop** taking your medicines for your asthma or CRSwNP once you have started EXDENSUR. These medicines (especially ones called corticosteroids) must be stopped gradually, under the direct supervision of your doctor.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, 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 EXDENSUR can pass into breast milk. If you are breast-feeding, you must check with your doctor before you use EXDENSUR.

Driving and using machines
EXDENSUR is unlikely to affect your ability to drive or use machines.

EXDENSUR contains polysorbates
This medicine contains 0.2 mg of polysorbate 80 per 100 mg dose. Polysorbates may cause allergic reactions. **Tell your doctor** if you have any known allergies.

EXDENSUR contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially "sodium-free".

3. How to use EXDENSUR

EXDENSUR is given by injection under the skin (*subcutaneous*).

The recommended dose

- **Asthma** — for adults and adolescents aged 12 years and older, the recommended dose is 100 mg. You will have **1 injection every 6 months**.

- **CRSwNP** — for adults, the recommended dose is 100 mg. You will have **1 injection every 6 months**.

How to use

Instructions for using the pre-filled syringe are given on the reverse of this leaflet.

Your doctor or nurse will decide if you or your caregiver can inject EXDENSUR. If appropriate, they will then give you or your caregiver training to show you the correct way to use EXDENSUR.

You can inject EXDENSUR under your skin in your stomach area (abdomen) or upper leg (thigh). Your caregiver can also inject EXDENSUR into your upper arm. Do not inject into areas where the skin is tender, bruised, red, or hard.

➔ Contact your doctor or nurse if you find it difficult to inject yourself, or if you have any concerns about whether you have injected correctly or given yourself a complete dose.

If you forget to use EXDENSUR
If your doctor or healthcare professional usually gives you your injection of EXDENSUR:
➔ contact your doctor or hospital as soon as possible to re-schedule your appointment.
If you or your caregiver usually give the injection of EXDENSUR, and you miss a dose:
➔ inject a dose of EXDENSUR as soon as possible. After that, continue EXDENSUR on your usual planned injection day.

If you miss a dose by 1 month or more:
➔ inject a dose of EXDENSUR then restart your 6-month injection schedule from the day you inject the missed dose.
If you are not sure what to do, ask your doctor, pharmacist or nurse.

Don't stop EXDENSUR without advice
Do not stop injections of EXDENSUR unless your doctor advises you to. Interrupting or stopping the treatment with EXDENSUR may cause your symptoms to come back.
If your symptoms get worse while receiving injections of EXDENSUR:
➔ 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.

Common (may affect **up to 1 in 10** people):
- itching (pruritus)
- headache, tiredness, or rash around the time of injection
- reactions at the site of injection such as pain, redness, swelling, or itching

Side effects that have been seen with similar medicines:
- severe allergic reactions such as anaphylaxis and angioedema (rash, swelling of the face, throat or mouth, fast heartbeat, sweating, difficulty in breathing, collapse or loss of consciousness).

➔ **Seek medical attention immediately** if you think you may be having a reaction.

➔ **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.**

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EXDENSUR

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

Do not use this medicine 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 a refrigerator (2°C - 8°C).

Do not freeze.

Do not shake.

Store in the original carton in order to protect from light.

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. After 7 days out of the refrigerator, dispose of the syringe according to local health and safety laws.

The pre-filled syringe must be used within 8 hours once the carton is opened. Discard if not used within 8 hours.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXDENSUR contains
- The active substance is depemokimab. Each mL of solution contains 100 mg of depemokimab.
- The other ingredients are histidine, histidine monohydrochloride, trehalose dihydrate, arginine hydrochloride, disodium edetate, polysorbate 80 (E 433), water for injections.

What EXDENSUR looks like and contents of the pack

EXDENSUR is supplied as a 1 mL colourless, yellow to brown, clear to opalescent solution in a single-use pre-filled syringe.

EXDENSUR is available in packs containing 1 pre-filled syringe.

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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Step by step instructions for use

EXDENSUR 100 mg solution for injection in pre-filled syringe
depemokimab
for subcutaneous use

This Instructions for Use contains information on how to inject EXDENSUR.

Read these sections first

Before using your EXDENSUR pre-filled syringe, it is important that your healthcare provider explains your EXDENSUR dosing instructions, and shows you (or your caregiver) how to use the syringe correctly.

Important information

Read all of these instructions before using your syringe. If you do not follow these instructions, you may not get all your medicine.

Do not use EXDENSUR syringe:
- if it has been frozen
- if it has been dropped or damaged
- if the security seal on the carton has been broken
- if the expiry date (EXP) has passed

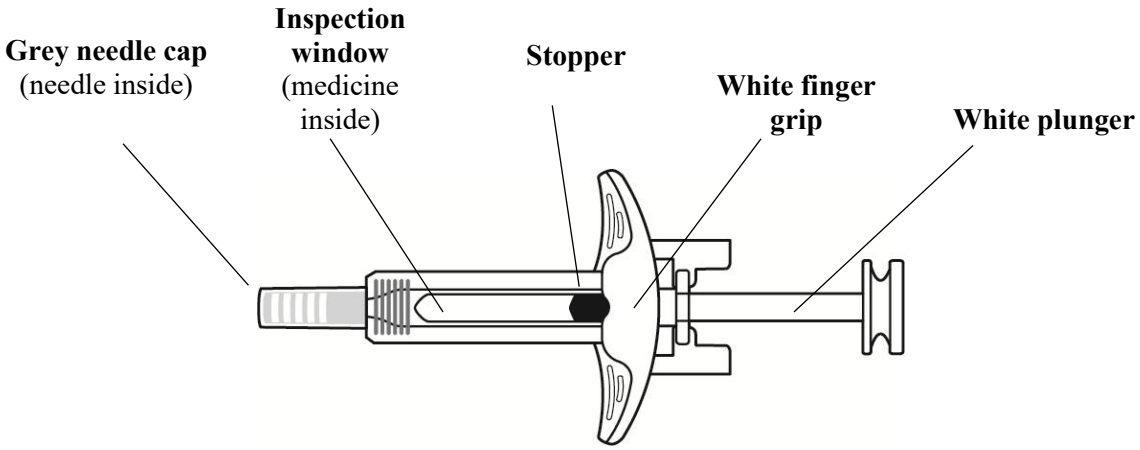
Do not:
- shake your EXDENSUR syringe
- share your syringe
- reuse your syringe
- expose your syringe to heat

If any of these happen, dispose of the EXDENSUR syringe according to local health and safety laws and use a new EXDENSUR syringe.

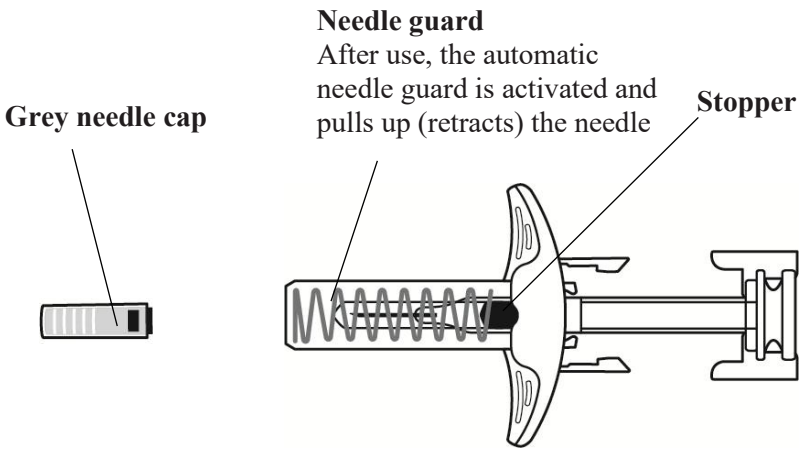
Keep out of the sight and reach of children. Contains small parts.

Get to know your EXDENSUR pre-filled syringe

Before use



After use



Storage

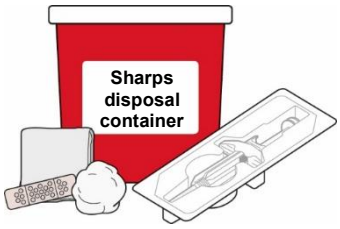
Store the syringe in its carton
Store EXDENSUR in a refrigerator (2°C - 8°C) in the original carton until you are ready to use it. **Do not** freeze.

An unopened carton of EXDENSUR may be kept at room temperature up to 30°C for a maximum of 7 days. After being brought to room temperature, EXDENSUR must be used within 7 days. After 7 days, dispose of the syringe according to local health and safety laws.

Once the syringe is removed from its carton
After the EXDENSUR syringe is out of the carton, it must be used within 8 hours or dispose of the syringe according to local health and safety laws. **Do not** place it back in the refrigerator.

A. Prepare

A1

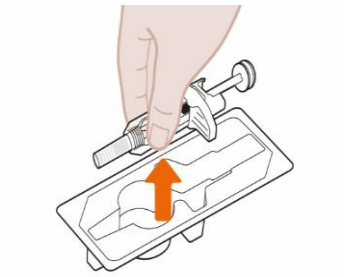


Gather supplies

Supplied
- EXDENSUR syringe

Not supplied
- Alcohol swab
- Cotton ball or gauze
- Adhesive plaster
- Sharps disposal container (see Section C for disposal instructions).

A2



Take the **syringe out** of the tray

Take the carton containing your syringe out of the refrigerator

- Holding the **middle** of the syringe (near the inspection window), carefully take the syringe out of the tray.
- **Do not** remove the grey needle cap at this step.

A3

Check the **expiry date** and the **medicine**

Check your pre-filled syringe

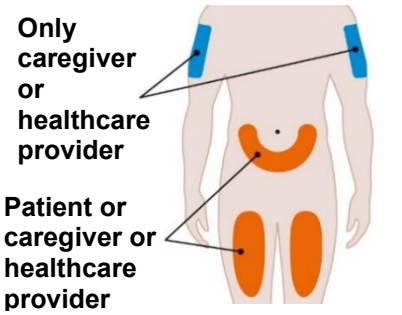
- Check the expiry date. **Do not** use if the expiry date has passed.
- Look at the medicine in the pre-filled syringe through the inspection window. The medicine should be clear and colourless to yellow to brown.
- **Do not** inject if the medicine is cloudy, discoloured, or has particles.
- It is normal to see air bubbles. You **do not** need to do anything about it.
- **Do not** shake the syringe.

A4

Wait 30 minutes

- **Do not** remove the grey needle cap.
- Place the syringe on a clean, flat surface away from direct sunlight and out of the sight and reach of children.
- **Wait 30 minutes** to bring to room temperature before you inject. Cold medicine is more painful to inject.
- **Do not** warm the syringe in a microwave, hot water, or direct sunlight.
- **Do not** use the syringe if it has been left out of the carton for more than 8 hours.

A5



Choose your injection site

- If you are giving yourself the injection, you can inject into your thighs or stomach (abdomen).
- A caregiver or healthcare provider can inject into the upper arm, thigh, or abdomen.
- **Do not** inject yourself in the upper arm, as it is more difficult to avoid syringe movement during the injection.
- **Do not** inject where the skin is bruised, tender, red, or hard.
- **Do not** inject within 5 cm of your navel (belly button).

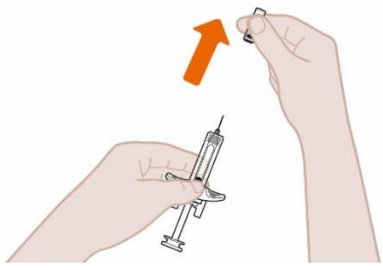
A6

Clean the injection site

- Wash your hands with soap and water.
- Clean the injection site with an alcohol swab. Allow skin to air dry.
- **Do not** fan or blow on the cleaned injection site.
- **Do not** touch the cleaned injection site again until you have finished your injection.

B. Inject

B1

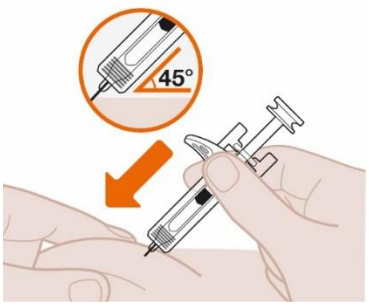


Pull off the grey needle cap

- Remove the grey needle cap from the syringe by pulling it straight off, away from the needle (as shown). It may take some force to remove the grey needle cap.
- **Do not** handle the syringe by the white plunger while removing the grey needle cap.
- **Do not** let the needle touch any surface.
- **Do not** touch the needle.
- **Do not** try to remove any air bubbles from the syringe.
- **Do not** put the grey needle cap back onto the syringe. This could cause a needle injury.

- Inject within 5 minutes after you remove the grey needle cap.

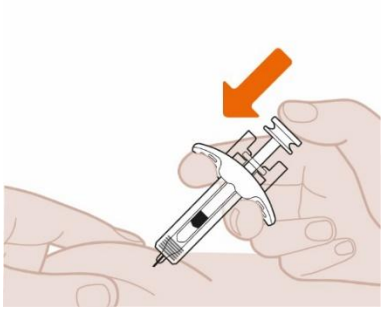
B2



Position the syringe at the injection site

- Use your free hand to gently pinch the skin around the cleaned injection site.
- Keep pinching the skin throughout the injection.
- **Do not** handle the syringe by the white plunger while inserting the needle into the pinched skin.
- Hold the **middle** of the syringe and insert the entire needle into the pinched skin at a 45 degree angle, as shown.

B3



Start the injection

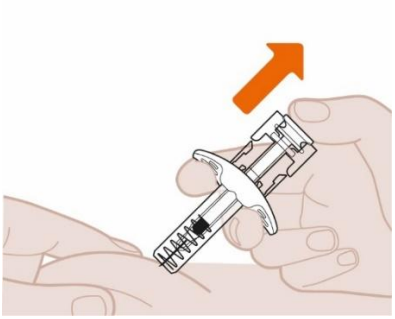
- Move your thumb to the white plunger and use your other fingers to hold onto the white finger grip, as shown.
- Slowly push down on the white plunger to inject the full dose.

B4

Fully press the white plunger

- Make sure the white plunger is pushed all the way down until the stopper reaches the bottom of the syringe and all of the medicine is injected.

B5



Slowly lift your thumb after the injection is complete

- Slowly lift your thumb up. This will allow the white plunger to come up and the needle to automatically pull up (retract) into the needle guard.
- After removing the syringe from the injection site, release the pinched skin.
- **Do not** rub the injection site.

- **Do not** put the grey needle cap back onto the syringe.
- There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive plaster if you need it.

C. Throw away

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