

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

Dupixent 300 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow solution, which is free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis.

Posology

The recommended dose of Dupixent for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection.

Dupixent can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Elderly patients (≥65 years)

No dose adjustment is recommended for elderly patients (see section 5.2).

Renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment

No data are available in patients with hepatic impairment (see section 5.2).

Body weight

No dose adjustment for body weight is recommended (see section 5.2).

Paediatric patients

The safety and efficacy of Dupixent in children below the age of 18 years have not been established (see section 5.2). No data are available.

Method of administration

Subcutaneous use

Dupixent is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used. For the initial 600 mg dose, administer two 300 mg Dupixent injections consecutively in different injection sites.

It is recommended to rotate the injection site with each injection. Dupixent should not be injected into skin that is tender, damaged or has bruises or scars.

A patient may self-inject Dupixent or the patient's caregiver may administer Dupixent if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of Dupixent prior to use according to the Instructions for Use (IFU) section in 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

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of Dupixent should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in clinical trials following the administration of Dupixent (section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupixent may influence the immune response against helminth infections by inhibiting IL-4/IL-13 signaling. Patients with pre-existing helminth infections should be treated before initiating Dupixent. If patients become infected while receiving treatment with Dupixent and do not respond to anti-helminth treatment, treatment with Dupixent should be discontinued until infection resolves.

Conjunctivitis related events

Patients treated with Dupixent who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination.

Comorbid asthma

Safety and efficacy of Dupixent have not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of Dupixent.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of concurrent use of Dupixent with live vaccines has not been studied.

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent), and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

Therefore, patients receiving Dupixent may receive concurrent inactivated or non-live vaccinations.

In a clinical study of AD patients, the effects of dupilumab on the PK of CYP substrates were evaluated. The data gathered from this study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of dupilumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Dupixent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue Dupixent therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dupixent has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes.

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9 % of the placebo group, 1.9 % of the Dupixent 300 mg Q2W group, 1.5 % of the Dupixent 300 mg QW group. In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6 % of the placebo + TCS group, 1.8 % of the Dupixent 300 mg Q2W + TCS group, and 2.9 % of the Dupixent 300 mg QW + TCS group.

Tabulated list of adverse reactions

The safety of Dupixent was evaluated in four randomized, double-blind, placebo-controlled studies and one dose-ranging study in patients with moderate-to-severe atopic dermatitis. In these 5 trials, 1689 subjects were treated with subcutaneous injections of Dupixent, with or without concomitant topical corticosteroids (TCS). A total of 305 patients were treated with Dupixent for at least 1 year.

Listed in Table 1 are adverse reactions observed in clinical trials presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 List of adverse reactions

System Organ Class	Frequency	Adverse Reaction
<i>Infections and infestations</i>	Common	Conjunctivitis Oral herpes
<i>Blood and lymphatic system disorders</i>	Common	Eosinophilia
<i>Immune system disorders</i>	Very rare	Serum sickness/serum sickness-like reactions
<i>Nervous system disorders</i>	Common	Headache
<i>Eye disorders</i>	Common	Conjunctivitis allergic Eye pruritus Blepharitis
<i>General disorders and administration site conditions</i>	Very common	Injection site reactions

Description of selected adverse reactions

Hypersensitivity

Very rare cases of serum sickness/serum sickness-like reactions have been reported following administration of Dupixent (see section 4.4).

Eczema herpeticum

Eczema herpeticum was reported in < 1 % of the Dupixent groups and in < 1 % of the placebo group in the 16-week monotherapy studies. In the 52-week Dupixent + TCS study, eczema herpeticum was reported in 0.2 % of the Dupixent + TCS group and 1.9 % of the placebo + TCS group.

Eosinophilia

Transient eosinophilia was reported in < 2 % of patients treated with Dupixent.

Infections

In the 16-week monotherapy clinical studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5 % of patients treated with Dupixent. In the 52-week CHRONOS study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with Dupixent.

Herpes zoster

Herpes zoster was reported in <0.1 % of the Dupixent groups and in <1 % of the placebo group in the 16-week monotherapy studies. In the 52-week Dupixent + TCS study, herpes zoster was reported in 1 % of the Dupixent + TCS group and 2 % of the placebo + TCS group.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with Dupixent.

ADA responses were not generally associated with impact on Dupixent exposure, safety, or efficacy. In the 52-week study, approximately 3 % of patients in the placebo group and 2 % of patients in the Dupixent group had anti-drug antibody (ADA) responses lasting more than 12 weeks. Among these patients, 0.7 % on placebo and 0.2 % treated with Dupixent also had neutralizing antibody responses, which were not generally associated with loss of efficacy.

In the overall exposure pool, less than 0.1 % of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (<0.1 %) associated with high ADA titers (see section 4.4).

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

There is no specific treatment for Dupixent overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

ATC code: **not yet assigned**

Mechanism of action

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R α / γ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R α /IL-13R α).

IL-4 and IL-13 are key type 2 (including Th2) cytokines involved in atopic dermatitis.

Pharmacodynamic effects

In clinical trials, treatment with dupilumab was associated with decreases from baseline in concentrations of type 2 immunity biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE and allergen-specific IgE in serum. A reduction of lactate dehydrogenase (LDH), a biomarker associated with AD disease activity and severity, was observed with Dupixent treatment.

Clinical efficacy and safety

The efficacy and safety of Dupixent as monotherapy and with concomitant topical corticosteroids were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, and CHRONOS) in 2119 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥ 3 , an Eczema Area and Severity Index (EASI) score ≥ 16 , and a minimum body surface area (BSA) involvement of ≥ 10 %. Eligible patients enrolled into the three studies had previous inadequate response to topical medication.

In all three studies, patients received 1) an initial dose of 600 mg Dupixent (two 300 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W); 2) an initial dose of 600 mg Dupixent on day 1, followed by 300 mg once weekly (QW); or 3) matching placebo. Dupixent was administered by subcutaneous (SC) injection in all studies. If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment (which included higher potency topical steroids or systemic immunosuppressants) at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

SOLO 1 enrolled 671 patients (224 to placebo, 224 to Dupixent 300 mg Q2W, and 223 to Dupixent 300 mg QW) and had a treatment period of 16 weeks.

SOLO 2 enrolled 708 patients (236 to placebo, 233 to Dupixent 300 mg Q2W, and 239 to Dupixent 300 mg QW) and had a treatment period of 16 weeks.

CHRONOS enrolled 740 patients (315 to placebo + topical corticosteroid (TCS), 106 to Dupixent 300 mg Q2W + TCS, and 319 to Dupixent 300 mg QW + TCS) and had a treatment period of 52 weeks. Patients received Dupixent or placebo with concomitant use of TCS starting at baseline using a standardized regimen. Patients were also permitted to use topical calcineurin inhibitors (TCI).

Endpoints

In all three pivotal studies, the co-primary endpoints were the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale and the proportion of patients with improvement of at least 75 % in EASI (EASI-75) from baseline to week 16. Other evaluated outcomes included the proportion of patients with improvement of at least 50 % and 90 % in EASI (EASI-50 and EASI-90, respectively), reduction in itch as measured by the peak pruritus Numerical Rating Scale (NRS), and percent change in the SCORing Atopic Dermatitis (SCORAD) scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS) scores. In CHRONOS, efficacy was also evaluated at week 52.

Baseline Characteristics

In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, the mean age was 38.3, the mean weight was 76.9 kg, 42.1% were female, 68.1% were white, 21.8% were Asian, and 6.8% were black. In these studies, 51.6 % of patients had a baseline IGA score of 3 (moderate AD), 48.3 % of patients had a baseline IGA of 4 (severe AD) and 32.4 % of patients had received prior systemic immunosuppressants. The baseline mean EASI score was 33.0, the baseline weekly averaged pruritus NRS was 7.4, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.5, the baseline mean DLQI was 15.0, and the baseline mean HADS total score was 13.3.

In the concomitant TCS study (CHRONOS), across all treatment groups, the mean age was 37.1, the mean weight was 74.5 kg, 39.7 % were female, 66.2 % were white, 27.2 % were Asian, and 4.6 % were black. In this study, 53.1 % of patients had a baseline IGA score of 3 and 46.9 % of patients had a baseline IGA of 4 and 33.6 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 32.5, the baseline weekly pruritus NRS was 7.3, the baseline mean SCORAD score was 66.4, the baseline mean POEM score was 20.1, the baseline mean DLQI was 14.5, and the baseline mean HADS total score was 12.7.

Clinical Response

16-Week Monotherapy Studies (SOLO 1 and SOLO 2)

In SOLO 1 and SOLO 2, from baseline to week 16, a significantly greater proportion of patients randomized to Dupixent achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥ 4 points on the pruritus NRS compared to placebo (see Table 2).

A significantly greater proportion of patients randomized to Dupixent achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥ 4 -point improvement as early as week 2; $p < 0.01$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 1 and Figure 2 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively up to week 16.

Table 2: Efficacy results of Dupixent monotherapy at Week 16 (FAS)

	SOLO 1 (FAS) ^a			SOLO 2 (FAS) ^a		
	Placebo	Dupixent 300 mg Q2W	Dupixent 300 mg QW	Placebo	Dupixent 300 mg Q2W	Dupixent 300 mg QW
<i>Patients randomised</i>	224	224	223	236	233	239
IGA 0 or 1 ^b , % responders ^c	10.3 %	37.9 % ^e	37.2 % ^e	8.5 %	36.1 % ^e	36.4 % ^e
EASI-50, % responders ^c	24.6 %	68.8 % ^e	61.0 % ^e	22.0 %	65.2 % ^e	61.1 % ^e
EASI-75, % responders ^c	14.7 %	51.3 % ^e	52.5 % ^e	11.9 %	44.2 % ^e	48.1 % ^e
EASI-90, % responders ^c	7.6 %	35.7 % ^e	33.2 % ^e	7.2 %	30.0 % ^e	30.5 % ^e
EASI, LS mean % change from baseline (+/- SE)	-37.6 % (3.28)	-72.3 % ^e (2.63)	-72.0 % ^e (2.56)	-30.9 % (2.97)	-67.1 % ^e (2.52)	-69.1 % ^e (2.49)
SCORAD, LS mean % change from baseline (+/- SE)	-29.0 % (3.21)	-57.7 % ^e (2.11)	-57.0 % ^e (2.11)	-19.7 % (2.52)	-51.1 % ^e (2.02)	-53.5 % ^e (2.03)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-26.1 % (3.02)	-51.0 % ^e (2.50)	-48.9 % ^e (2.60)	-15.4 % (2.98)	-44.3 % ^e (2.28)	-48.3 % ^e (2.35)
<i>Number of patients with baseline pruritus NRS score ≥ 4</i>	212	213	201	221	225	228
Pruritus NRS (≥4-point improvement) , % responders ^{c, d}	12.3 %	40.8 % ^e	40.3 % ^e	9.5%	36.0 % ^e	39.0 % ^e

LS = least squares; SE= standard error

^a Full analysis set (FAS) includes all patients randomized.

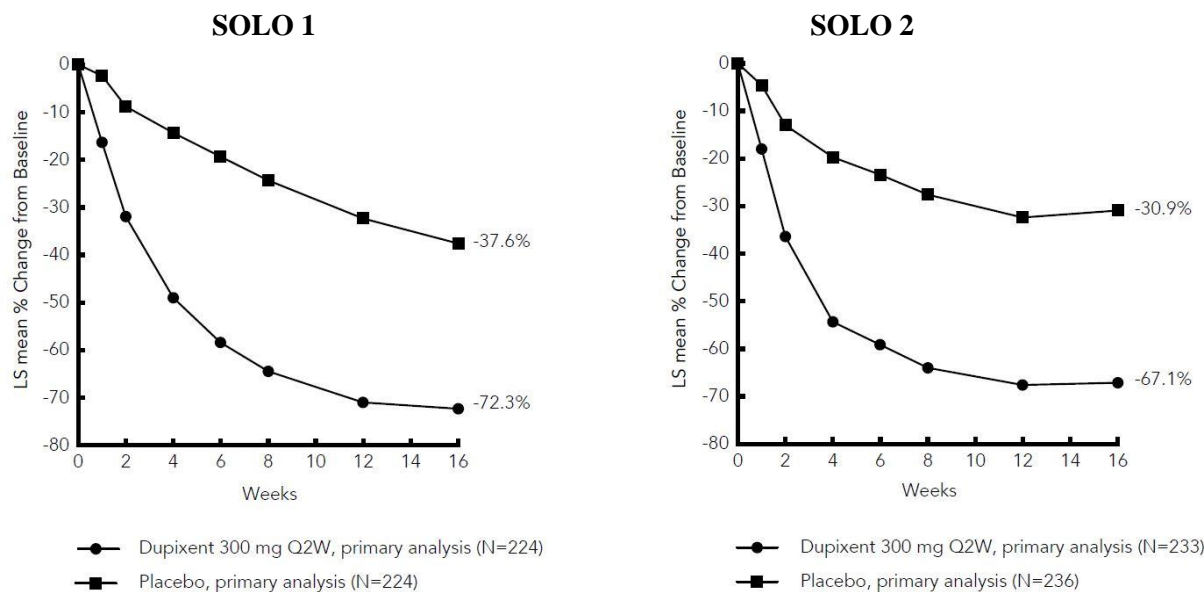
^b Responder was defined as a patient with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0-4 IGA scale.

^c Patients who received rescue treatment or with missing data were considered as non-responders.

^d a significantly greater proportion of patients on Dupixent had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 (p <0.01).

^e p-value <0.0001

Figure 1: Mean percent change from baseline in EASI in SOLO 1^a and SOLO 2^a (FAS)^b

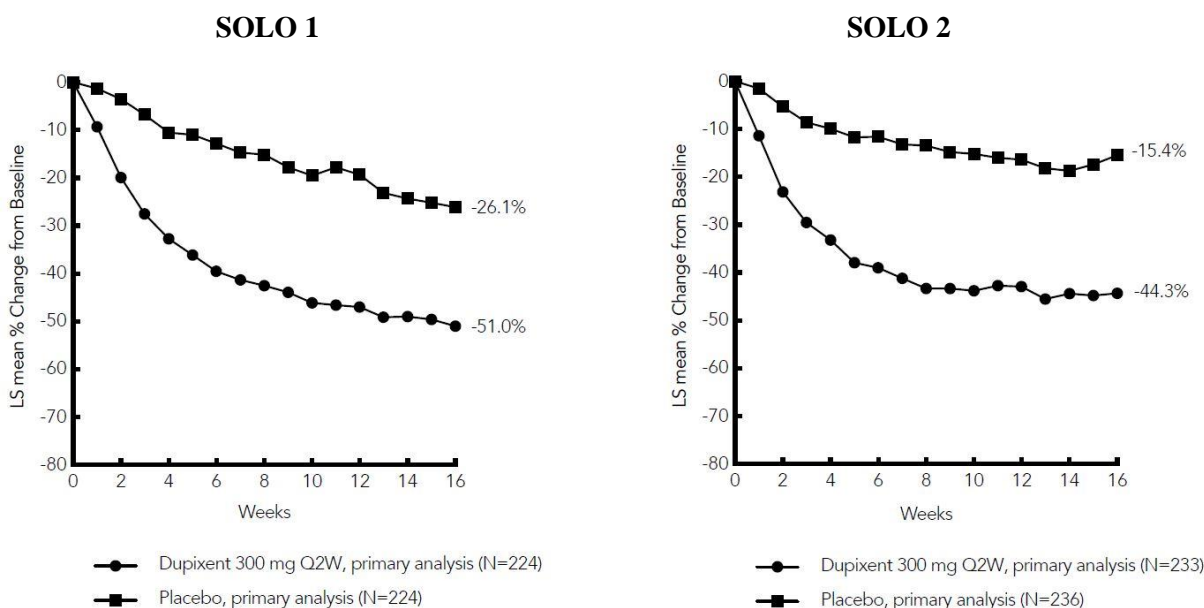


LS = least squares

^a In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

^b Full analysis set (FAS) includes all patients randomized.

Figure 2: Mean percent change from baseline in NRS in SOLO 1^a and SOLO 2^a (FAS)^b



LS = least squares

^a In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders

^b Full analysis set (FAS) includes all patients randomized.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in SOLO 1 and SOLO 2 were consistent with the results in the overall study population.

52-Week Concomitant TCS Study (CHRONOS)

In CHRONOS, a significantly greater proportion of patients randomized to Dupixent 300 mg Q2W + TCS achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥ 4 points on the pruritus NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 3).

A significantly greater proportion of patients randomized to Dupixent + TCS achieved a rapid improvement in the pruritus NRS compared to placebo + TCS (defined as ≥ 4 -point improvement as early as week 2; $p < 0.05$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period. The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 3 and Figure 4 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively, up to Week 52 in CHRONOS.

Table 3: Efficacy results of Dupixent with concomitant TCS^a at Week 16 and Week 52 in CHRONOS

	Week 16 (FAS) ^b			Week 52 (FAS Week 52) ^b		
	Placebo + TCS	Dupixent 300 mg Q2W + TCS	Dupixent 300 mg QW + TCS	Placebo + TCS	Dupixent 300 mg Q2W + TCS	Dupixent 300 mg QW + TCS
Patients randomized	315	106	319	264	89	270
IGA 0 or 1 ^c , % responders ^d	12.4 %	38.7 % ^f	39.2 % ^f	12.5 %	36.0 % ^f	40.0 % ^f
EASI-50, % responders ^d	37.5 %	80.2 % ^f	78.1 % ^f	29.9 %	78.7 % ^f	70.0 % ^f
EASI-75, % responders ^d	23.2 %	68.9 % ^f	63.9 % ^f	21.6 %	65.2 % ^f	64.1 % ^f
EASI-90, % responders ^d	11.1 %	39.6 % ^f	43.3 % ^f	15.5 %	50.6 % ^f	50.7 % ^f
EASI, LS mean % change from baseline (+/- SE)	-48.4 % (3.82)	-80.5 % ^f (6.34)	-81.5 % ^f (5.78)	-60.9 % (4.29)	-84.9 % ^g (6.73)	-87.8 % ^h (6.19)
SCORAD, LS mean % change from baseline (+/- SE)	-36.2 % (1.66)	-63.9 % ^f (2.52)	-65.9 % ^f (1.49)	-47.3 % (2.18)	-69.7 % ^f (3.06)	-70.4 % ^f (1.72)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-30.3 % (2.36)	-56.6 % ^f (3.95)	-57.1 % ^f (2.11)	-31.7 % (3.95)	-57.0 % ⁱ (6.17)	-56.5 % ^f (3.26)
Number of patients with baseline pruritus NRS score ≥ 4	299	102	295	249	86	249
Pruritus NRS (≥ 4 -point improvement), % responders ^{d, e}	19.7 %	58.8 % ^f	50.8 % ^f	12.9 %	51.2 % ^f	39.0 % ^f

LS = least squares; SE = standard error

^a All patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.

^b Full analysis set (FAS) includes all patients randomized. FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

^c Responder was defined as a patient with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0-4 IGA scale.

^d Patients who received rescue treatment or with missing data were considered as non-responders.

^e a significantly greater proportion of patients on Dupixent had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 (p <0.05).

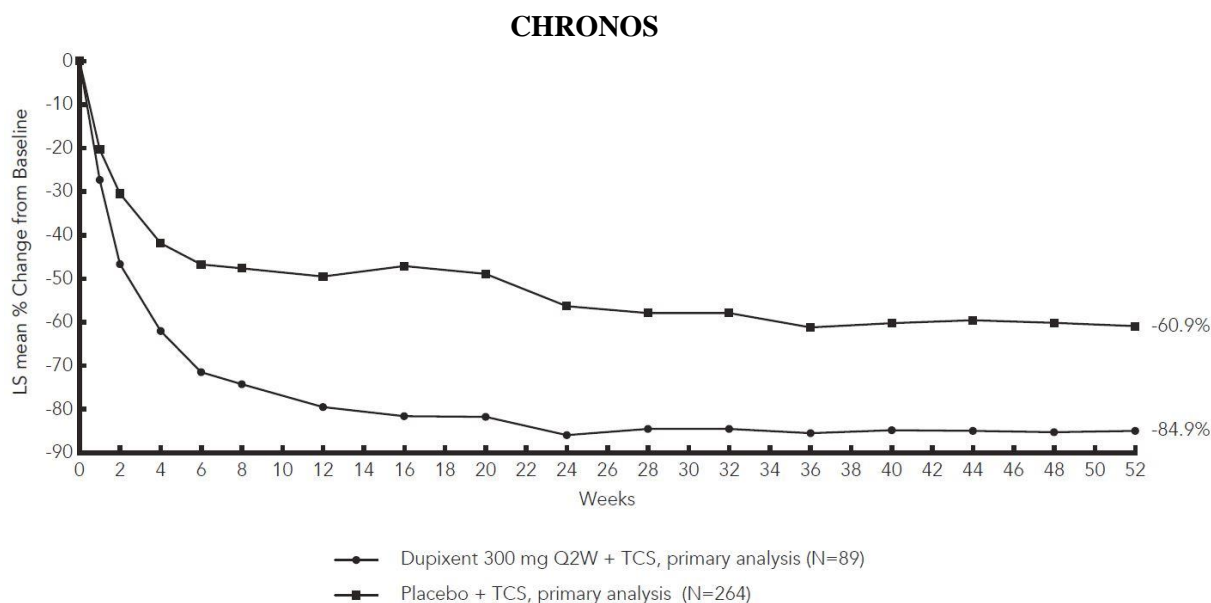
^f p-value <0.0001

^g p-value = 0.0015

^h p-value = 0.0003

ⁱ p-value = 0.0005

Figure 3: Mean percent change from baseline in EASI in CHRONOS^a (FAS Week 52)^b

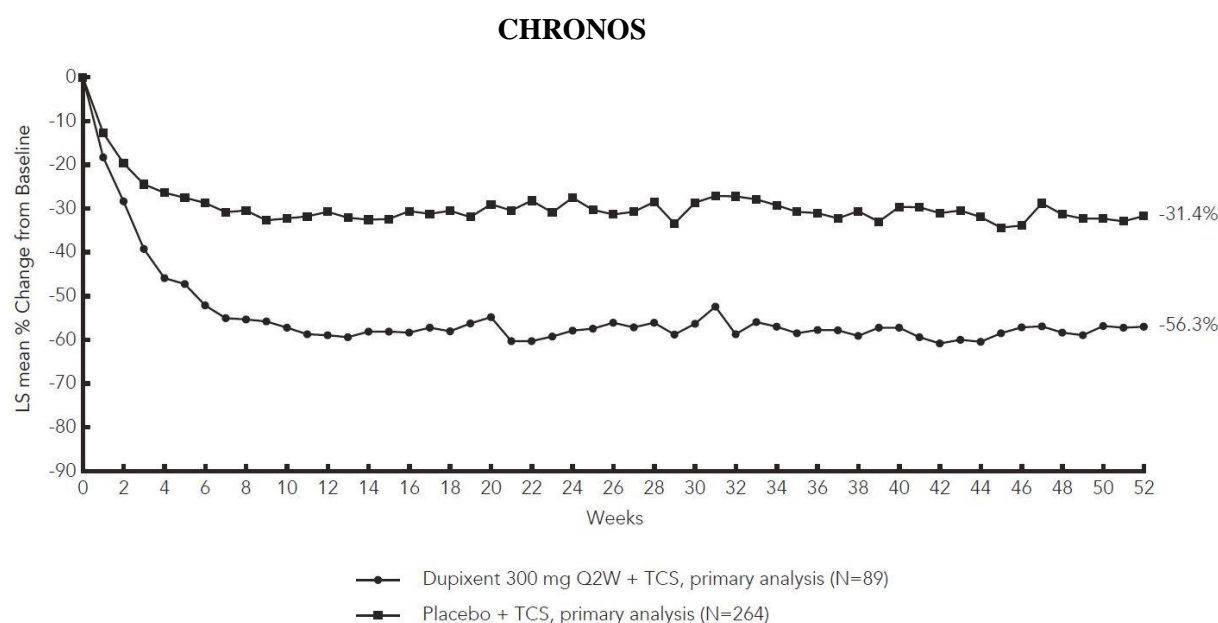


LS = least squares

^aIn the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

^bFAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

Figure 4: Mean percent change from baseline in NRS in CHRONOS^a (FAS Week 52)^b



LS = least squares

^aIn the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.

^bFAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in CHRONOS were consistent with the results in the overall study population.

Clinical Response in Patients Not Adequately Controlled with, Intolerant to, or for whom Ciclosporin Treatment was Inadvisable (CAFE study)

CAFE study evaluated the efficacy of Dupixent compared to placebo during a 16-week treatment period, administered with concomitant TCS, in adult patients with AD who are not adequately controlled with, or are intolerant to, oral ciclosporin, or when this treatment is currently contraindicated or not medically advisable.

A total of 325 patients were enrolled, with 210 patients who were previously exposed to ciclosporin and 115 patients who have never been exposed to ciclosporin because ciclosporin treatment was medically inadvisable. The mean age was 38.4 years, 38.8 % were female, the baseline mean EASI score was 33.1, the mean BSA was 55.7, the baseline weekly average pruritus NRS was 6.4, the baseline mean SCORAD score was 67.2, and the baseline mean DLQI was 13.8.

The primary endpoint was the proportion of patients with EASI-75 at week 16. Primary and secondary endpoints for the 16 week CAFE study are summarized in table 4.

Table 4: Results of the primary and secondary endpoints in CAFE study

	Placebo + TCS	Dupixent 300 mg Q2W + TCS	Dupixent 300 mg QW+TCS
<i>Patients randomised</i>	108	107	110
EASI-75, % responders	29.6 %	62.6 %	59.1 %
EASI, LS mean % change from baseline (+/- SE)	-46.6 (2.76)	-79.8 (2.59)	-78.2 (2.55)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-25.4 % (3.39)	-53.9 % (3.14)	-51.7 % (3.09)
SCORAD, LS mean % change from baseline (+/- SE)	-29.5 % (2.55)	-62.4 % (2.48)	-58.3 % (2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

In the subgroup of patients resembling the CAFE study population within the 52 week CHRONOS study, 69.6 % of Dupixent 300 mg Q2W-treated patients reached EASI-75 vs 18.0 % placebo-treated patients at week 16, and 52.4 % of Dupixent 300 mg Q2W-treated vs 18.6 % placebo-treated at week 52. In this subset, the percent change of pruritus NRS from baseline was -51.4 % vs -30.2 % at week 16 and -54.8 % vs -30.9 % at week 52, for the Dupixent 300 mg Q2W and placebo groups respectively.

Maintenance and Durability of Response (SOLO CONTINUE study)

To evaluate maintenance and durability of response, subjects treated with Dupixent for 16 weeks in SOLO 1 and SOLO 2 studies who achieved IGA 0 or 1 or EASI-75 were re-randomized in SOLO CONTINUE study to an additional 36-week treatment of Dupixent or placebo, for a cumulative 52-week study treatment. Endpoints were assessed at weeks 51 or 52.

The co-primary endpoints were the difference between baseline (week 0) and week 36 in percent change in EASI from SOLO 1 and SOLO 2 studies baseline and percentage of patients with EASI-75 at week 36 in patients with EASI-75 at baseline.

Patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300 mg Q2W or 300 mg QW) showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner.

Primary and secondary endpoints for the 52 week SOLO CONTINUE study are summarized in table 5.

Table 5: Results of the primary and secondary endpoints in SOLO CONTINUE study

	Placebo	Dupilumab 300 mg		
	N=83	Q8W N=84	Q4W N=86	Q2W/QW N=169
Co-Primary Endpoints				
LS mean change (SE) between baseline and week 36 in percent change in EASI Score from Parent Study baseline	21.7 (3.13)	6.8*** (2.43)	3.8*** (2.28)	0.1*** (1.74)
Percent of patients with EASI-75 at week 36 for patients with EASI-75 at baseline, n (%)	24/79 (30.4%)	45/82* (54.9%)	49/84** (58.3%)	116/162*** (71.6%)
Key Secondary Endpoints				
Percent of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA (0,1) at baseline, n (%)	18/63 (28.6)	32/64† (50.0)	41/66** (62.1)	89/126*** (70.6)
Percent of patients with IGA (0,1) at week 36 in the subset of patients with IGA (0,1) at baseline, n (%)	9/63 (14.3)	21/64† (32.8)	29/66** (43.9)	68/126*** (54.0)
Percent of patients whose peak pruritus NRS increased by ≥3 points from baseline to week 35 in the subset of patients with peak pruritus NRS ≤7 at baseline, n (%)	56/80 (70.0)	45/81 (55.6)	41/83† (49.4)	57/168*** (33.9)

†P<0.05, *P<0.01, **P<0.001, ***P≤0.0001

In SOLO CONTINUE, a trend for increased treatment-emergent ADA positivity with increased dosing intervals was observed. Treatment-emergent ADA: QW: 1.2%; Q2W: 4.3%; Q4W: 6.0%; Q8W: 11.7%. ADA responses lasting more than 12 weeks: QW: 0.0%; Q2W: 1.4%; Q4W: 0.0%; Q8W: 2.6%.

Quality of Life/Patient-Reported Outcomes

In both monotherapy studies (SOLO 1 and SOLO 2), both Dupixent 300 mg Q2W and 300 mg QW groups significantly improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 16 weeks compared to placebo. A significantly larger proportion of patients administered Dupixent groups had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥4 points improvement) from baseline to week 16 compared to placebo group. In addition, anxiety and depression symptoms as measured by the HADS total score were significantly reduced in the Dupixent groups compared to placebo at 16 weeks. In a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the Dupixent groups achieved HADS-anxiety and HADS-depression scores <8 at week 16 compared to placebo (See Table 6).

Table 6: Additional secondary endpoint results of Dupixent monotherapy at Week 16

	Monotherapy					
	SOLO 1 at Week 16			SOLO 2 at Week 16		
	Placebo	Dupixent 300 mg Q2W	Dupixent 300 mg QW	Placebo	Dupixent 300 mg Q2W	Dupixent 300 mg QW
<i>Patients randomized</i>	224	224	223	236	233	239
DLQI, LS mean change from baseline (SE)	-5.3 (0.50)	-9.3 ^a (0.40)	-9.0 ^a (0.40)	-3.6 (0.50)	-9.3 ^a (0.38)	-9.5 ^a (0.39)
POEM, LS mean change from baseline (SE)	-5.1 (0.67)	-11.6 ^a (0.49)	-11.0 ^a (0.50)	-3.3 (0.55)	-10.2 ^a (0.49)	-11.3 ^a (0.52)
HADS, LS mean change from baseline (SE)	-3.0 (0.65)	-5.2 ^b (0.54)	-5.2 ^b (0.51)	-0.8 (0.44)	-5.1 ^a (0.39)	-5.8 ^a (0.38)
<i>Number of patients with DLQI ≥4 at baseline</i>	213	209	209	225	223	234
DLQI (≥4-point improvement), % responders	30.5 %	64.1 % ^a	58.4 % ^a	27.6 %	73.1 % ^a	62.0 % ^a
<i>Number of patients with POEM ≥4 at baseline</i>	223	222	222	234	233	239
POEM (≥4-point improvement), % responders	26.9 %	67.6 % ^a	63.1 % ^a	24.4 %	71.7 % ^a	64.0 % ^a
<i>Number of patients with HADS-anxiety ≥8 or HADS-depression ≥8 at baseline</i>	97	100	102	115	129	136
Patients achieving HADS-anxiety and HADS-depression score <8, %	12.4 %	41.0 % ^a	36.3 % ^b	6.1 %	39.5 % ^a	41.2 % ^a

LS = least squares; SE = standard error

^a p-value <0.0001^b p-value <0.001

In the concomitant TCS study (CHRONOS), Dupixent 300 mg Q2W + TCS and Dupixent 300 mg QW + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 52 weeks compared to placebo + TCS. A larger proportion of patients administered Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥4-point improvement) from baseline to week 52 compared to the placebo + TCS. In addition, Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS reduced anxiety and depression as measured

by the HADS total score at 52 weeks compared to placebo + TCS. In a post-hoc analysis in a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥ 8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients in the Dupixent 300 mg Q2W + TCS and 300 mg QW + TCS groups achieved HADS-anxiety and HADS-depression scores < 8 at week 52 compared to placebo + TCS (See Table 7).

Table 7: Other secondary endpoint results of Dupixent with concomitant TCS at Week 16 and Week 52 in CHRONOS

	Concomitant Use of TCS					
	CHRONOS at Week 16			CHRONOS at Week 52		
	Placebo	Dupixent 300 mg Q2W + TCS	Dupixent 300 mg QW + TCS	Placebo +TCS	Dupixent 300 mg Q2W + TCS	Dupixent 300 mg QW + TCS
<i>Patients randomized</i>	315	106	319	264	89	270
DLQI, LS mean change from baseline (SE)	-5.8 (0.34)	-10.0 ^a (0.50)	-10.7 ^a (0.31)	-7.2 (0.40)	-11.4 ^a (0.57)	-11.1 ^a (0.36)
POEM, LS mean change from baseline (SE)	-5.3 (0.41)	-12.7 ^a (0.64)	-12.9 ^a (0.37)	-7.0 (0.57)	-14.2 ^a (0.78)	-13.2 ^a (0.45)
HADS, LS mean change from baseline (SE)	-4.0 (0.37)	-4.9 (0.58)	-5.4 ^c (0.35)	-3.8 (0.47)	-5.5 ^c (0.71)	-5.9 ^b (0.42)
<i>Number of patients with DLQI ≥ 4 at baseline</i>	300	100	311	254	85	264
DLQI (≥ 4 -point improvement), % responders	43.0 %	81.0 % ^a	74.3 % ^a	30.3 %	80.0 % ^a	63.3 % ^a
<i>Number of patients with POEM ≥ 4 at baseline</i>	312	106	318	261	89	269
POEM (≥ 4 -point improvement), % responders	36.9 %	77.4 % ^a	77.4 % ^a	26.1 %	76.4 % ^a	64.7 % ^a
<i>Number of patients with HADS-anxiety ≥ 8 or HADS-depression ≥ 8 at baseline</i>	148	59	154	133	53	138

Patients achieving HADS-anxiety and HADS-depression <8, %	26.4 %	47.5 % ^c	47.4 % ^b	18.0 %	43.4 % ^b	44.9 % ^a
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LS = least squares; SE = standard error

^a p-value <0.0001

^b p-value <0.001

^c p-value <0.05

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Dupixent in atopic dermatitis in one or more subset of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After a single subcutaneous (SC) dose of 75-600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is estimated to be 64 %, as determined by a population pharmacokinetics (PK) analysis.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose every other week. Across clinical trials, the mean \pm SD steady-state trough concentrations ranged from 73.3 \pm 40.0 mcg/mL to 79.9 \pm 41.4 mcg/mL for 300 mg dose administered every other week.

Distribution

A volume of distribution for dupilumab of approximately 4.6 L was estimated by population PK analysis, indicating that dupilumab is distributed primarily in the vascular system.

Biotransformation

Specific metabolism studies were not conducted because dupilumab is a protein. Dupilumab is expected to degrade to small peptides and individual amino acids.

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates. After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population PK analysis, was 10 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Linearity/non-linearity

Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time curve, increases with dose in a greater than proportional manner following single SC doses from 75-600 mg.

Special populations

Gender

Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis.

Elderly patients

Of the 1472 patients with atopic dermatitis exposed to Dupixent in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Age was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis. However, there were only 61 patients over 65 years of age included in this analysis.

Race

Race was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab by population PK analysis.

Hepatic impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. Very limited data are available in patients with severe renal impairment.

Body Weight

Dupilumab trough concentrations were lower in subjects with higher body weight with no meaningful impact on efficacy.

Paediatric patients

The pharmacokinetics of dupilumab in paediatric patients has not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints) and toxicity to reproduction and development.

The mutagenic potential of dupilumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity studies have not been conducted with dupilumab. An evaluation of the available evidence related to IL-4R α inhibition and animal toxicology data with surrogate antibodies does not suggest an increased carcinogenic potential for dupilumab.

During a reproductive toxicology study conducted in monkeys, using a surrogate antibody specific to the monkey IL-4R α , no fetal abnormalities were observed at dosages that saturate the IL-4R α .

An enhanced pre- and post-natal developmental study revealed no adverse effects in maternal animals or their offspring up to 6 months post-partum/post-birth.

Fertility studies conducted in male and female mice using a surrogate antibody against IL-4R α showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine hydrochloride
L-histidine
Polysorbate 80
Sodium acetate
Acetic acid
Sucrose
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

15 months.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. If the carton needs to be removed permanently from refrigerator, the date of removal may be recorded on the outer carton. After removal from the refrigerator, Dupixent must be used within 14 days or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

6.5 Nature and contents of container

2 ml solution in a siliconised type-1 clear glass pre-filled syringe with or without needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Pack size:

- 1 pre-filled syringe
- 2 pre-filled syringes
- Multipack containing 3 (3 packs of 1) pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The instructions for the preparation and administration of Dupixent in a pre-filled syringe are given in the package leaflet.

The solution should be clear to slightly opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.

After removing the pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting Dupixent.

The pre-filled syringe should not be exposed to heat or direct sunlight and should not be shaken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, place the pre-filled syringe into a puncture-resistant container and discard as required by local regulations. Do not recycle the container. Keep the container out of sight and reach of children.

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/001
EU/1/17/1229/002
EU/1/17/1229/003
EU/1/17/1229/004
EU/1/17/1229/005
EU/1/17/1229/006
EU/1/17/1229/007
EU/1/17/1229/008

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 <http://www.ema.europa.eu>

ANNEX II

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

Name and address of the manufacturer(s) of the biological active substance(s)

REGENERON PHARMACEUTICALS INC.

81 Columbia Turnpike

RENSSELAER

NEW YORK 12144

UNITED STATES

Name and address of the manufacturer(s) responsible for batch release

SANOFI WINTHROP INDUSTRIE

1051 Boulevard Industriel,

76580 LE TRAIT,

FRANCE

Sanofi-Aventis Deutschland GmbH

Brüningstrasse 50

Industriepark Hoechst

65926 FRANKFURT AM MAIN

GERMANY

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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
OUTER CARTON
Pre-filled syringe 300 mg**

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

2 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Do not shake
Open here

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
Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/001 1 pre-filled syringe

EU/1/17/1229/002 2 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON
Pre-filled syringe 300 mg - Multipack (contains Blue Box)**

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 3 (3 packs of 1) pre-filled syringes

Multipack: 6 (3 packs of 2) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Do not shake
Open here

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
Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/003 3 pre-filled syringes (3 packs of 1)

EU/1/17/1229/004 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INNER CARTON
Pre-filled syringe 300 mg - Multipack (without Blue Box)**

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

2 pre-filled syringes

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only

Read the package leaflet before use.

Subcutaneous use

Do not shake

Open here

**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

Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/003 3 pre-filled syringes (3 packs of 1)

EU/1/17/1229/004 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL
Pre-filled syringe 300 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dupixent 300 mg injection
dupilumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2 ml

6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON
Pre-filled syringe with needle shield 300 mg**

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe with needle shield
2 pre-filled syringes with needle shield

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Do not shake
Open here

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
Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/005 1 pre-filled syringe with needle shield

EU/1/17/1229/006 2 pre-filled syringes with needle shield

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON**

Pre-filled syringe with needle shield 300 mg - Multipack (contains Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 3 (3 packs of 1) pre-filled syringes with needle shield

Multipack: 6 (3 packs of 2) pre-filled syringes with needle shield

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Subcutaneous use
Do not shake
Open here

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

Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/007 3 pre-filled syringes with needle shield (3 packs of 1)

EU/1/17/1229/008 6 pre-filled syringes with needle shield (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INNER CARTON**

Pre-filled syringe with needle shield 300 mg - Multipack (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 300 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe with needle shield

2 pre-filled syringes with needle shield

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only

Read the package leaflet before use.

Subcutaneous use

Do not shake

Open here

**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

Date of removal from the refrigerator: / /

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Time out of refrigeration should not exceed a maximum of 14 days at temperature below 25 °C.

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

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**

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1229/007 3 pre-filled syringes with needle shield (3 packs of 1)

EU/1/17/1229/008 6 pre-filled syringes with needle shield (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Dupixent 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL

Pre-filled syringe with needle shield 300 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dupixent 300 mg injection
dupilumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dupixent 300 mg solution for injection in pre-filled syringe dupilumab

▼ 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 Dupixent is and what it is used for
2. What you need to know before you use Dupixent
3. How to use Dupixent
4. Possible side effects
5. How to store Dupixent
6. Contents of the pack and other information

1. What Dupixent is and what it is used for

Dupixent contains the active substance dupilumab.

Dupilumab is a monoclonal antibody (a type of specialised protein) that blocks the action of proteins called IL-4 and IL-13. Both play a major role in causing the signs and symptoms of atopic dermatitis.

Dupixent is used to treat adults with moderate-to-severe atopic dermatitis, also known as atopic eczema. Dupixent may be used with eczema medicines that you apply to the skin or it may be used on its own.

Using Dupixent for atopic dermatitis (atopic eczema) can improve the condition of your skin and reduce itching. Dupixent has also been shown to improve symptoms of pain, anxiety, and depression associated with atopic dermatitis. In addition, Dupixent helps improve your sleep disturbance and overall quality of life.

2. What you need to know before you use Dupixent

Do not use Dupixent

- if you are allergic to dupilumab or any of the other ingredients of this medicine (listed in section 6).
- if you think you may be allergic, or you are not sure, ask your doctor, pharmacist or nurse for advice before using Dupixent.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Dupixent:

Allergic reactions

Very rarely, Dupixent can cause serious side effects, including allergic (hypersensitivity) reactions. You must look out for signs of these conditions (i.e. fever, general ill feeling, swollen lymph nodes, hives, itching, joint pain, skin rash) while you are taking Dupixent.

Stop using Dupixent and tell your doctor or get medical help immediately if you notice any signs of an allergic reaction. Such signs are listed under “Serious side effects” in section 4.

Parasitic (intestinal parasites) infection

Dupixent may weaken your resistance to infections caused by parasites. If you already have a parasitic infection it should be treated before you start treatment with Dupixent. Check with your doctor if you have diarrhea, gas, upset stomach, greasy stools, and dehydration which could be a sign of a parasitic infection. If you live in a region where these infections are common or if you are travelling to such a region check with your doctor.

Asthma

If you have asthma and are taking asthma medicines, do not change or stop your asthma medicine without talking to your doctor. Talk to your doctor before you stop Dupixent.

Eye problems

Talk to your doctor if you have any new or worsening eye problems, including eye pain or changes in vision.

Children and adolescents

Dupixent is not recommended in children and adolescents below the age of 18 years.

Other medicines and Dupixent

Tell your doctor or pharmacist

- if you are using, have recently used or might use any other medicines.
- if you have recently had or are due to have a vaccination.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. The effects of this medicine in pregnant women are not known; therefore it is preferable to avoid the use of Dupixent in pregnancy unless your doctor advises to use it.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you will breast-feed or use Dupixent. You should not do both.

Driving and using machines

Dupixent is unlikely to influence your ability to drive and use machines.

Dupixent contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 300 mg dose, i.e., it is essentially “sodium-free”.

3. How to use Dupixent

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dupixent is given by injection under your skin (subcutaneous injection). You and your doctor or nurse should decide if you should inject Dupixent yourself.

Inject Dupixent yourself only after you have been trained by your doctor or nurse. A caregiver may also give you your Dupixent injection after proper training.

Each syringe contains one dose of Dupixent (300 mg). Do not shake the syringe.

Read the “Instructions for Use” for the syringe carefully before using Dupixent.

How much Dupixent is given and for how long

Your doctor will decide how much Dupixent you need and for how long. Dupixent is given by injection under the skin (subcutaneous injection).

The recommended first dose is 600 mg (two 300-mg injections), followed by 300 mg given every two weeks by subcutaneous injection.

If you use more Dupixent than you should

If you use more Dupixent than you should or the dose has been given too early, talk to your doctor, pharmacist or nurse.

If you forget to use Dupixent

If you have forgotten to inject a dose of Dupixent, talk to your doctor, pharmacist or nurse.

If you stop using Dupixent

Do not stop using Dupixent without speaking to your doctor first.

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.

Dupixent can cause serious side effects, including very rare allergic (hypersensitivity) reactions; the signs of allergic reaction may include:

- fever
- general ill feeling
- swollen lymph nodes
- hives
- itching
- joint pain
- skin rash

If you develop an allergic reaction, stop using Dupixent and talk to your doctor right away.

Other side effects

Very Common (may affect more than 1 in 10 people):

- injection site reactions (i.e. redness, swelling, and itching)

Common (may affect up to 1 in 10 people):

- headache
- eye dryness, redness and itching
- eyelid itching, redness and swelling
- eye infection
- cold sores (on lips and skin)

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 Dupixent

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 to 8°C). If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. If you need to permanently remove the carton from the refrigerator, write down the date of removal in the space provided on the outer carton, and use Dupixent within 14 days.

Store in the original carton to protect from light.

Do not use this medicine if you notice that the medicine is cloudy, discoloured, or has particles in it. Do not throw away any medicines via wastewater or household waste. Ask your doctor, pharmacist or nurse 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 Dupixent contains

- The active substance is dupilumab.
- Each pre-filled syringe contains 300 mg of dupilumab in 2 ml solution for injection (injection).
- The other ingredients are L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, acetic acid, sucrose, water for injections.

What Dupixent looks like and contents of the pack

Dupixent is a clear to slightly opalescent, colourless to pale yellow solution supplied in a glass pre-filled syringe with or without needle shield.

Dupixent is available in a pack containing 1 or 2 pre-filled syringes or in a pack containing 3 (3 packs of 1) or 6 (3 packs of 2) pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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54, rue La Boétie
75008 Paris
France

Manufacturer

SANOFI WINTHROP INDUSTRIE
1051 Boulevard Industriel,
76580 LE TRAIT,
FRANCE

Sanofi-Aventis Deutschland GmbH
Brüningstrasse 50
Industriepark Hoechst
65926 FRANKFURT AM MAIN
GERMANY

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

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Sanofi Belgium
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Sanofi Oy
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United Kingdom

Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

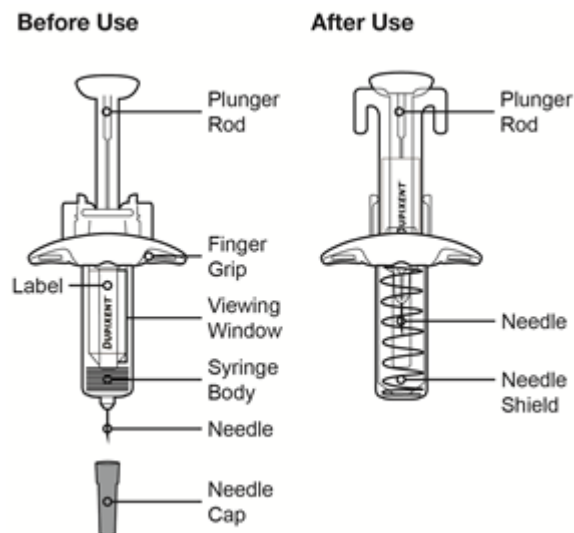
<http://www.ema.europa.eu>

<----->

Dupixent 300 mg solution for injection in a pre-filled syringe with needle shield dupilumab

Instructions for use

The parts of the Dupixent pre-filled syringe with needle shield are shown in this picture.



Important information

This device is a single-use pre-filled syringe. It contains 300 mg of Dupixent for injection under the skin (subcutaneous injection).

You must not try to give yourself or someone else the injection unless you have received training from your healthcare professional.

- Read all of the instructions carefully before using the syringe.
- Check with your healthcare professional how often you will need to inject the medicine.
- Ask your healthcare professional to show you the right way to use the syringe before you inject for the first time.
- Change the injection site for each injection.
- **Do not** use the syringe if it has been dropped on a hard surface or damaged.
- **Do not** use the syringe if the needle cap is missing or not securely attached.
- **Do not** touch the plunger rod until you are ready to inject.
- **Do not** inject through clothes.
- **Do not** get rid of any air bubbles in the syringe.
- To help prevent accidental needle injury, each pre-filled syringe has a needle shield that is automatically activated to cover the needle after you have given your injection.
- **Never** pull back on the plunger rod.
- **Do not** re-use the syringe.

How to Store Dupixent

- Keep the syringe(s) out of the reach of children.
- Keep unused syringes in the original carton and store in the refrigerator between 2°C and 8°C.
- **Do not** keep Dupixent at room temperature (<25°C) for more than 14 days. If you need to permanently remove the carton from the refrigerator, write down the date of removal in the space provided on the outer carton, and use Dupixent within 14 days.
- **Do not** shake the syringe at any time.
- **Do not** heat the syringe.

- **Do not** freeze the syringe.
- **Do not** place the syringe into direct sunlight.

Step 1: Remove

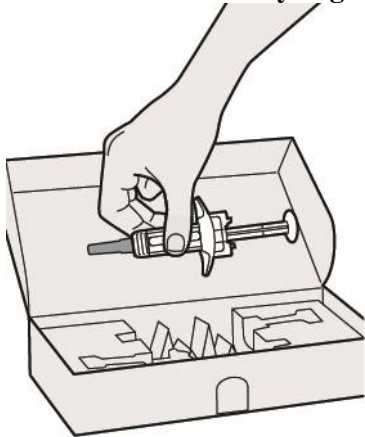
Remove the syringe from the carton by holding the middle of the syringe body.



Do not pull off the needle cap until you are ready to inject.



Do not use the syringe if it has been damaged.



Step 2: Prepare

Ensure you have the following:

- the Dupixent pre-filled syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 13)

**Items not included in the carton*

Look at the label:

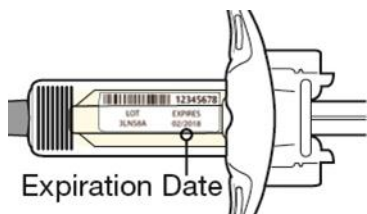
- Check the expiry date.
- Check that you have the correct product and dose.



Do not use the syringe if the expiry date has passed.



Do not keep Dupixent at room temperature for more than 14 days.



Step 3: Inspect

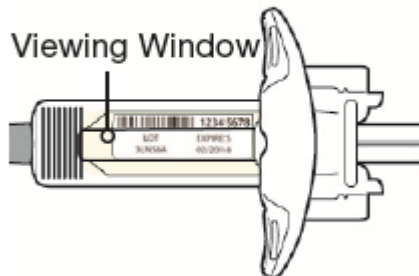
Look at the medicine through the viewing window on the syringe:

Check if the liquid is clear and colourless to pale yellow.

Note: You may see an air bubble; this is normal.



Do not use the syringe if the liquid is discoloured or cloudy, or if it contains flakes or particles.



Step 4: Wait 45 minutes

Lay the syringe on a flat surface for at least 45 minutes and let it get to room temperature naturally.



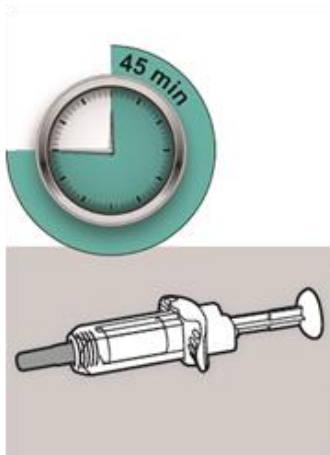
Do not heat the syringe.



Do not place the syringe in direct sunlight.



Do not keep Dupixent at room temperature for more than 14 days.



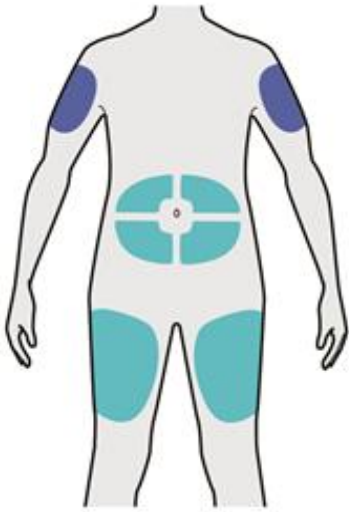
Step 5: Choose



Select the injection site.

- You can inject into your thigh or belly (stomach), except for the 5 cm around your navel.
- If somebody else gives you the injection, they can also use your upper arm.
- Change the injection site for each injection.



Do not inject into skin that is tender, damaged or has bruises or scars.



-  - Self-injection or by caregiver
-  - Injection by caregiver only

Step 6: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.



Do not touch the injection site again or blow on it before the injection.



Step 7: Pull

Hold the syringe in the middle of the syringe body with the needle pointing away from you and pull off the needle cap.

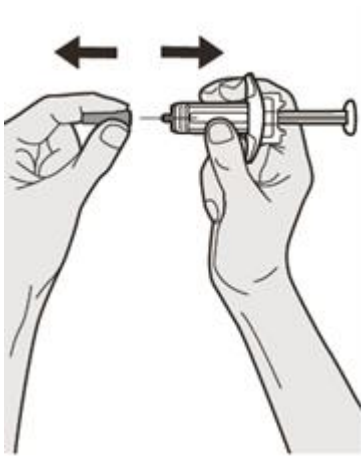


Do not put the needle cap back on.



Do not touch the needle.

Inject your medicine immediately after removing the needle cap.



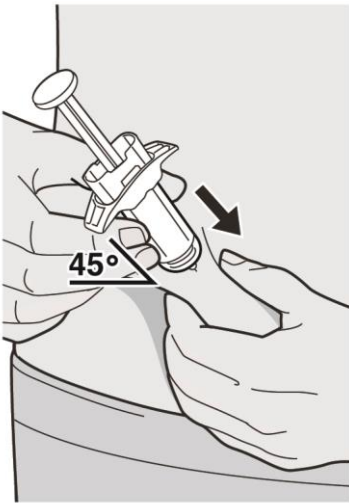
Step 8: Pinch

Pinch a fold of skin at the injection site, as shown in the picture.



Step 9: Insert

Insert the Needle completely into the fold of skin at roughly a 45° angle.



Step 10: Push

Relax the pinch.

Push the plunger rod down slowly and steadily as far as it will go until the syringe is empty.

Note: You will feel some resistance. This is normal.



Step 11: Remove

Keep pressing down on the plunger and remove the needle from the skin at the same angle it was inserted.



Do not put the needle cap back on.



Step 12: Release

Once the needle is out of the skin, lift your thumb from the plunger, which pulls back the needle up into the needle shield.

Lightly press a cotton ball or gauze on the injection site if you see any blood.

 **Do not rub your skin after the injection.**

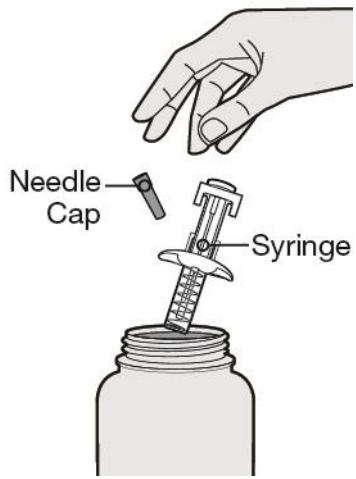


Step 13: Dispose

Dispose of the syringe and the needle cap in a puncture-resistant container.

 **Do not put the needle cap back on.**

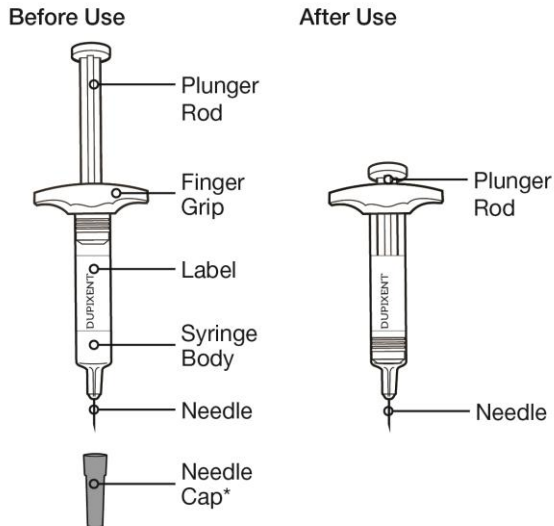
Always keep the container out of the reach of children.



Dupixent 300 mg solution for injection in a pre-filled syringe dupilumab

Instructions for use

The parts of the Dupixent pre-filled syringe are shown in this picture.



*The device may have either a soft or hard Needle Cap.

Important information

This device is a single-use pre-filled syringe. It contains 300 mg of Dupixent for injection under the skin (subcutaneous injection).

You must not try to give yourself or someone else the injection unless you have received training from your healthcare professional.

- Read all of the instructions carefully before using the syringe.
- Check with your healthcare professional how often you will need to inject the medicine.
- Ask your healthcare professional to show you the right way to use the syringe before you inject for the first time.
- Change the injection site for each injection.
- **Do not** use the syringe if it has been damaged.
- **Do not** use the syringe if the needle cap is missing or not securely attached.
- **Do not** touch the plunger rod until you are ready to inject.
- **Do not** inject through clothes.
- **Do not** get rid of any air bubbles in the syringe.
- **Never** pull back on the plunger rod.
- **Do not** re-use the syringe.

How to Store Dupixent

- Keep the syringe(s) out of the reach of children.
- Keep unused syringes in the original carton and store in the refrigerator between 2°C and 8°C.
- **Do not** keep Dupixent at room temperature (<25°C) for more than 14 days. If you need to permanently remove the carton from the refrigerator, write down the date of removal in the space provided on the outer carton, and use Dupixent within 14 days.
- **Do not** shake the syringe at any time.
- **Do not** heat the syringe.
- **Do not** freeze the syringe.
- **Do not** place the syringe into direct sunlight.

Step 1: Remove

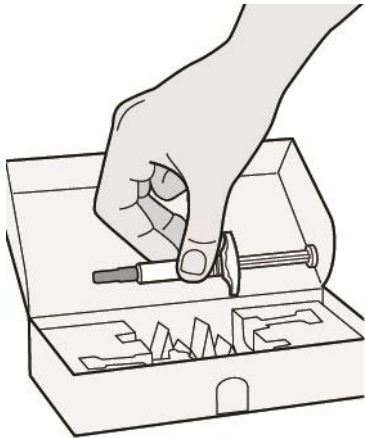
Remove the syringe from the carton by holding the middle of the syringe body.



Do not pull off the needle cap until you are ready to inject.



Do not use the syringe if it has been damaged.



Step 2: Prepare

Ensure you have the following:

- the Dupixent pre-filled syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 12)

**Items not included in the carton*

Look at the label:

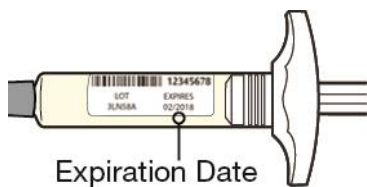
- Check the expiry date.
- Check that you have the correct product and dose.



Do not use the syringe if the expiry date has passed.



Do not keep Dupixent at room temperature for more than 14 days.



Step 3: Inspect

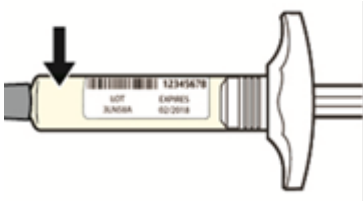
Look at the medicine in the syringe:

Check if the liquid is clear and colourless to pale yellow.

Note: You may see an air bubble; this is normal.



Do not use the syringe if the liquid is discoloured or cloudy, or if it contains flakes or particles.



Step 4: Wait 45 minutes

Lay the syringe on a flat surface for at least 45 minutes and let it get to room temperature naturally.



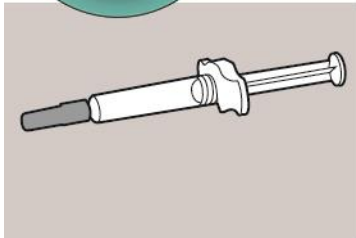
Do not heat the syringe.



Do not place the syringe in direct sunlight.



Do not keep Dupixent at room temperature for more than 14 days.



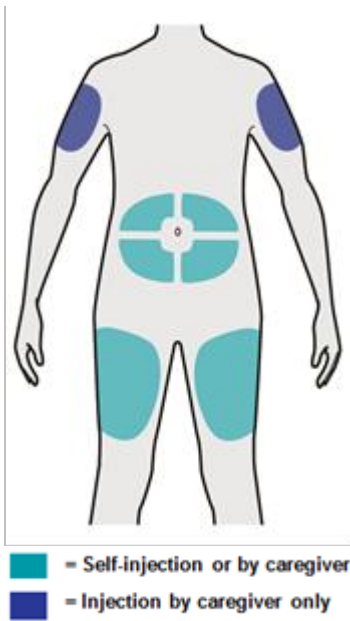
Step 5: Choose

Select the injection site.

- You can inject into your thigh or belly (stomach), except for the 5 cm around your navel.
- If somebody else gives you the injection, they can also use your upper arm.
- Change the injection site for each injection.



Do not inject into skin that is tender, damaged or has bruises or scars.



Step 6: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.



Do not touch the injection site again or blow on it before the injection.



Step 7: Pull

Hold the syringe in the middle of the syringe body with the needle pointing away from you and pull off the needle cap.

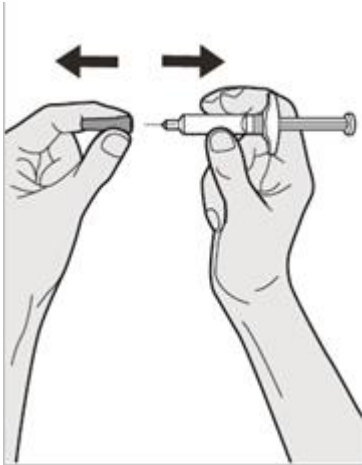


Do not put the needle cap back on.



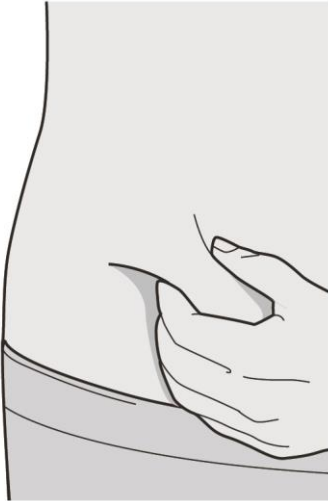
Do not touch the needle.

Inject your medicine immediately after removing the needle cap.



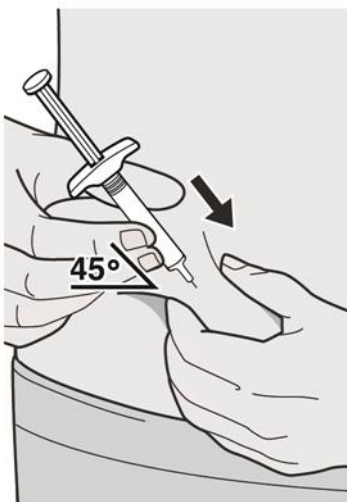
Step 8: Pinch

Pinch a fold of skin at the injection site, as shown in the picture.



Step 9: Insert

Insert the needle into the fold of skin at roughly a 45° angle.



Step 10: Push

Relax the pinch.

Push the plunger rod down slowly and steadily as far as it will go until the syringe is empty.

Note: You will feel some resistance. This is normal.



Step 11: Remove

Pull the needle out of the skin at the same angle it was inserted.

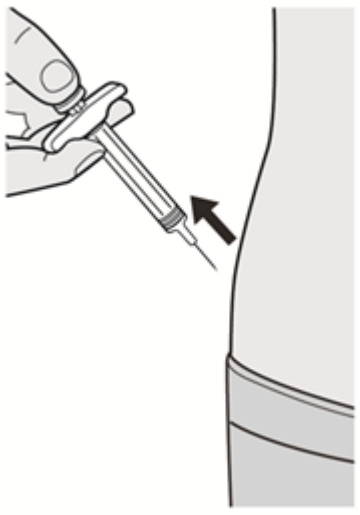


Do not put the needle cap back on.

Lightly press a cotton ball or gauze on the injection site if you see any blood.



Do not rub your skin after the injection.



Step 12: Dispose

Dispose of the syringe and the needle cap in a puncture-resistant container.



Do not put the needle cap back on.

Always keep the container out of the reach of children.

