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

Dupilumab 300 mg solution for injection in pre-filled syringe

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

Atopic Dermatitis

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Asthma

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated (see section 4.1).

Posology

Atopic Dermatitis

Adults
The recommended dose of dupilumab 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.

Adolescents
The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of dupilumab for subcutaneous administration in adolescent patients 12 years to 17 years of age with atopic dermatitis

Body Weight of Patient	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Dupilumab 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.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Asthma

The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is:

- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.
- For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as subcutaneous injection.

Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). Steroid reductions should be accomplished gradually (see section 4.4).

Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Missed dose

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

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 for patients with asthma 12 years of age and older or in adults with atopic dermatitis (see section 5.2).

For patients 12 to 17 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (< 60 kg) or 300 mg (≥ 60 kg).

Paediatric patients
The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established (see section 5.2). No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 12 years have not been established (see section 5.2). No data are available.

Method of administration

Subcutaneous use

Dupilumab 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, two 300 mg injections should be administered consecutively in different injection sites.

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

A patient may self-inject dupilumab or the patient's caregiver may administer dupilumab 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 dupilumab 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

Dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus.

Systemic, topical, or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be

associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. This should be taken into consideration to determine type 2 status in patients taking oral corticosteroids (see section 5.1).

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 dupilumab should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program following the administration of dupilumab. Anaphylactic reaction has been reported very rarely in the asthma development program following the administration of dupilumab (section 4.8).

Eosinophilic conditions

Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with dupilumab in adult patients who participated in the asthma development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy.

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab 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 dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves.

Conjunctivitis related events

Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (section 4.8).

Atopic dermatitis patients with comorbid asthma

Patients on dupilumab for moderate-to-severe atopic dermatitis who also have 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 dupilumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed, see section 4.5. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

Sodium content

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

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 dupilumab may receive concurrent inactivated or non-live vaccinations. For information on live vaccines see section 4.4.

In a clinical study of AD patients, the effects of dupilumab on the pharmacokinetics (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.

An effect of dupilumab on the PK of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on dupilumab pharmacokinetics on patients with moderate to severe asthma.

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). Dupilumab 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 dupilumab 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

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

4.8 Undesirable effects

Atopic dermatitis

Adults with atopic dermatitis

Summary of the safety profile

The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program (see section 4.4).

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 dupilumab 300 mg Q2W group, 1.5 % of the dupilumab 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 dupilumab 300 mg Q2W + TCS group, and 2.9 % of the dupilumab 300 mg QW + TCS group.

Tabulated list of adverse reactions

The safety of dupilumab 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, 1,689 subjects were treated with subcutaneous injections of dupilumab, with or without concomitant topical corticosteroids (TCS). A total of 305 patients were treated with dupilumab for at least 1 year.

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: List of adverse reactions in atopic dermatitis

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

Adolescents with atopic dermatitis

The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of dupilumab in these patients followed through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of dupilumab was assessed in an open-label extension study in patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in AD-1526 study. The long-term safety profile of dupilumab observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

Summary of the safety profile

The most common adverse reaction was injection site erythema. Anaphylactic reaction has been reported very rarely in the asthma development program (see section 4.4).

In DRI12544 and QUEST studies, the proportion of patients who discontinued treatment due to adverse events was 4.3% of the placebo group, 3.2% of the dupilumab 200 mg Q2W group, and 6.1% of the dupilumab 300 mg Q2W group.

Tabulated list of adverse reactions

A total of 2,888 adult and adolescent patients with moderate-to-severe asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). Of these, 2,678 had a history of 1 or more severe exacerbations in the year prior to enrolment despite regular use of medium-to-high dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 patients with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE).

Listed in Table 3 are adverse reactions observed in asthma clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: List of adverse reactions in asthma

MedDRA System Organ Class	**Frequency**	**Adverse Reaction**
Immune system disorders	Very rare	Anaphylactic reaction
General disorders and administration site conditions	Very common Common Common Common	Injection site erythema Injection site oedema Injection site pain Injection site pruritus

Description of selected adverse reactions in atopic dermatitis and asthma indications

Hypersensitivity
Very rare cases of serum sickness/serum sickness-like reactions and anaphylactic reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and related events
Conjunctivitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis recovered or were recovering during the treatment period. Among asthma patients frequency of conjunctivitis was low and similar between dupilumab and placebo (see section 4.4).

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

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophil counts declined to near baseline levels during study treatment.

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 2 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients.

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

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

Anti-Drug-Antibodies (ADA) responses were not generally associated with impact on dupilumab exposure, safety, or efficacy.

Approximately 6 % of patients with atopic dermatitis or asthma who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies.

Approximately 9 % of patients with asthma who received dupilumab 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4 % exhibited persistent ADA responses and approximately 4 % had neutralizing antibodies.

Approximately 5 % of patients in the placebo groups in the 52 week studies were also positive for antibodies to dupilumab; approximately 2 % exhibited persistent ADA response and approximately 1% had neutralizing antibodies.

Less than 0.4 % 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).

Paediatric population

The safety profile observed in adolescents aged 12 to 17 years in atopic dermatitis clinical trials was similar to that seen in adults.

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in the 52 week QUEST study. The safety profile observed was similar to that seen in adults.

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 dupilumab 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: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH05

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-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis and asthma. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.

Pharmacodynamic effects

In atopic dermatitis 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 dupilumab treatment.

In asthma clinical trials, dupilumab treatment markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin in asthma subjects relative to placebo. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Clinical efficacy and safety in atopic dermatitis

Adults with atopic dermatitis

The efficacy and safety of dupilumab 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 2,119 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 dupilumab (two 300 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W); 2) an initial dose of 600 mg dupilumab on day 1, followed by 300 mg once weekly (QW); or 3) matching placebo. Dupilumab 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 dupilumab 300 mg Q2W, and 223 to dupilumab 300 mg QW) and had a treatment period of 16 weeks.

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

CHRONOS enrolled 740 patients (315 to placebo + topical corticosteroid (TCS), 106 to dupilumab 300 mg Q2W + TCS, and 319 to dupilumab 300 mg QW + TCS) and had a treatment period of 52 weeks. Patients received dupilumab 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 dupilumab 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 4).

A significantly greater proportion of patients randomized to dupilumab 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 4: Efficacy results of dupilumab monotherapy at week 16 (FAS)

	SOLO 1 (FAS)[a]			SOLO 2 (FAS)[a]		
	Placebo	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo**	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**
Patients randomised	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)
Number of patients with baseline pruritus NRS score ≥ 4	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.

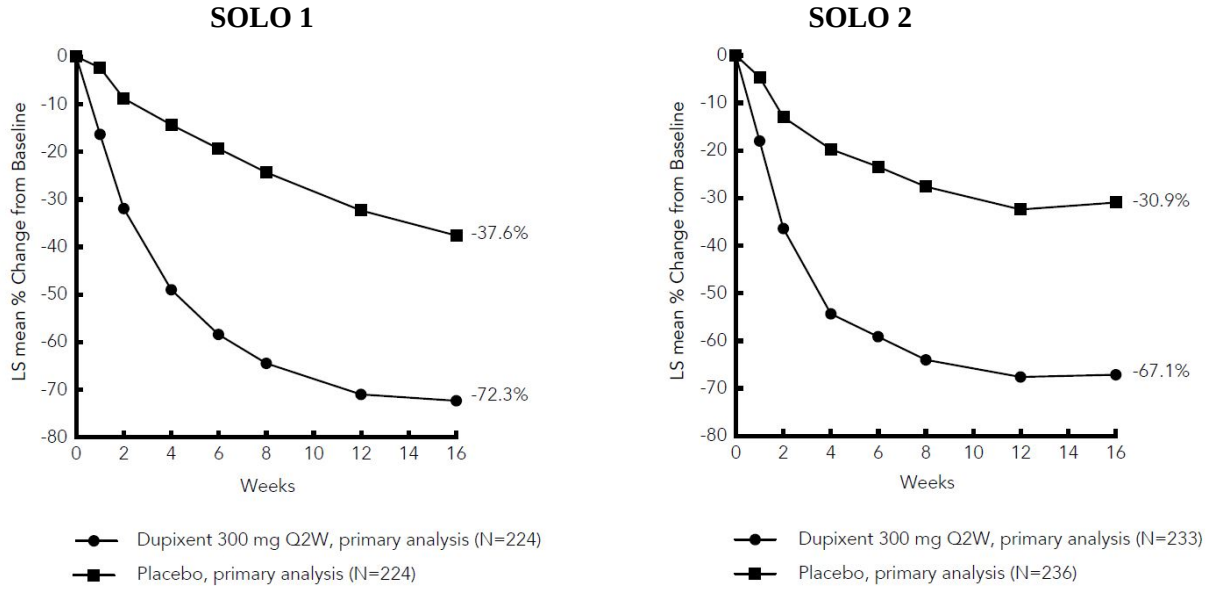
[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.

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

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

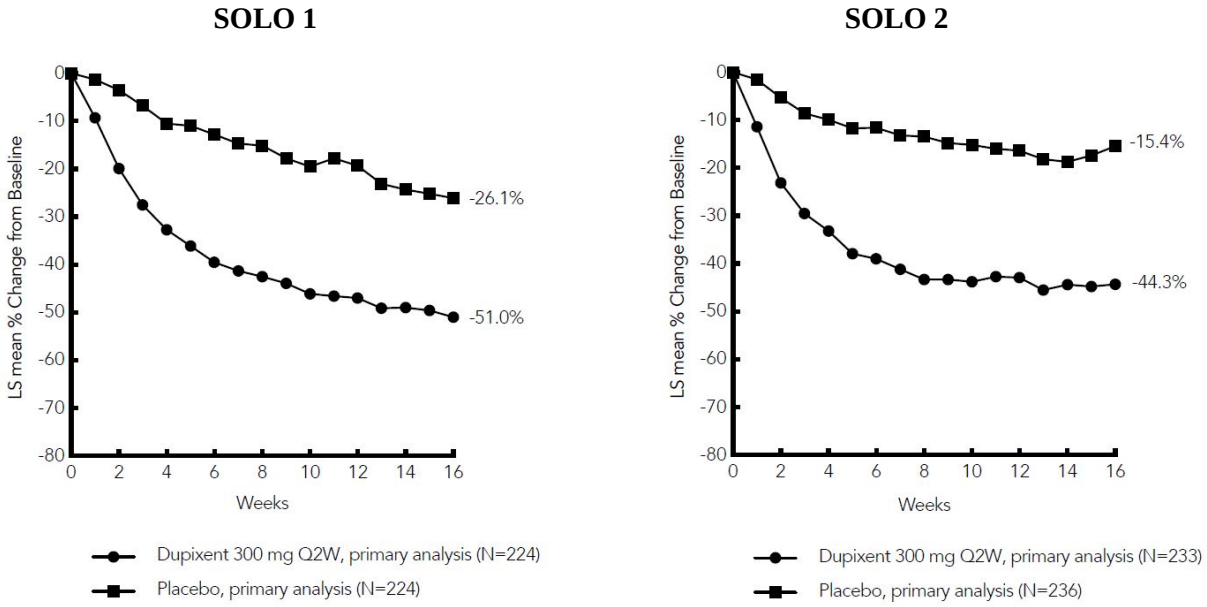
[e] p-value <0.0001

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 dupilumab 300 mg Q2W + TCS achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥ 4 points on the pruritis NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 5).

A significantly greater proportion of patients randomized to dupilumab + 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.

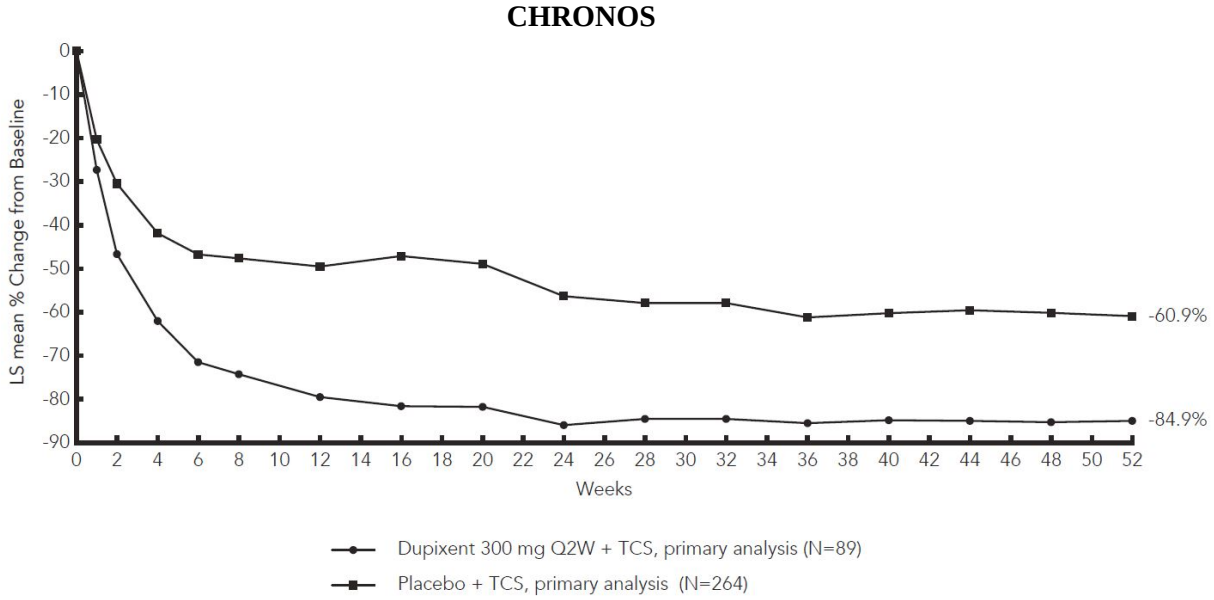
Figure 3 and Figure 4 show the mean percent change from baseline in EASI and the mean percent change from baseline in NRS, respectively, up to week 52 in CHRONOS.

Table 5: Efficacy results of dupilumab with concomitant TCS[a] at Week 16 and Week 52 in CHRONOS

	Week 16 (FAS)[b]			**Week 52 (FAS Week 52)[b]**		
	Placebo + TCS	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**	**Placebo + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 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]

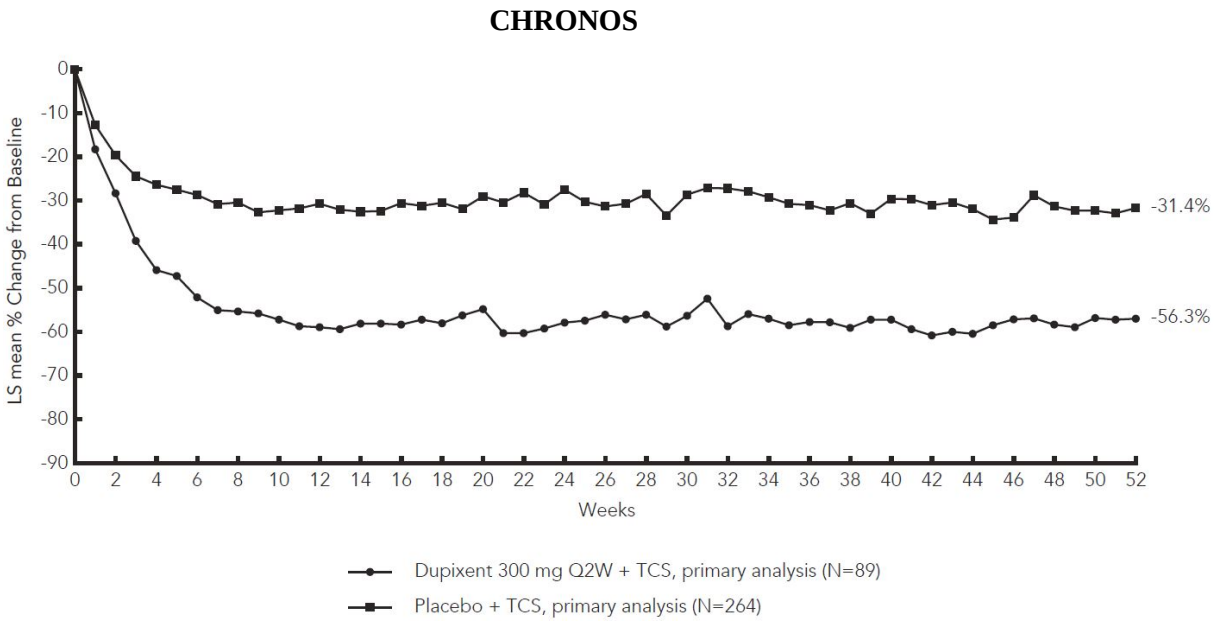
LS = least squares; SE = standard error
[a] All patients were on background topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.
[b] Full analysis set (FAS) includes all patients randomized. FAS week 52 includes all patients randomized at least one year before 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 dupilumab 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
[a] In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.
[b] FAS 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
[a]In the primary analyses of the efficacy endpoints, patients who received rescue treatment or with missing data were considered non-responders.
[b]FAS 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 dupilumab 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 pruritis 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 6.

Table 6: Results of the primary and secondary endpoints in CAFE study

	Placebo + TCS	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW+TCS**
Patients randomised	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)

(all p values <0.0001)

In the subgroup of patients resembling the CAFE study population within the 52 week CHRONOS study, 69.6 % of dupilumab 300 mg Q2W-treated patients reached EASI-75 vs 18.0 % placebo-treated patients at week 16, and 52.4 % of dupilumab 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 dupilumab 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 dupilumab 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 dupilumab 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 7.

Table 7: 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 Atopic Dermatitis

In both monotherapy studies (SOLO 1 and SOLO 2), both dupilumab 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 dupilumab 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 dupilumab 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 dupilumab groups achieved HADS-anxiety and HADS-depression scores < 8 at week 16 compared to placebo (See Table 8).

Table 8: Additional secondary endpoint results of dupilumab monotherapy at Week 16

	Monotherapy					
	SOLO 1 at Week 16			SOLO 2 at Week 16		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
Patients randomized	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)
Number of patients with DLQI ≥4 at baseline	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]
Number of patients with POEM ≥4 at baseline	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]
Number of patients with HADS-anxiety ≥ 8 or HADS-depression ≥ 8 at baseline	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), dupilumab 300 mg Q2W + TCS and dupilumab 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 dupilumab 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, dupilumab 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 dupilumab 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 9).

Table 9: Other secondary endpoint results of dupilumab with concomitant TCS at Week 16 and Week 52 in CHRONOS

	Concomitant Use of TCS					
	CHRONOS at Week 16			**CHRONOS at Week 52**		
	Placebo	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**	**Placebo +TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**
Patients randomized	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)
Number of patients with DLQI ≥4 at baseline	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]
Number of patients with POEM ≥4 at baseline	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]
Number of patients with HADS-anxiety ≥ 8 or HADS-depression ≥ 8 at baseline	148	59	154	133	53	138
Patients achieving HADS-anxiety	26.4 %	47.5 %[c]	47.4 %[b]	18.0 %	43.4 %[b]	44.9 %[a]

and HADS-depression < 8, %						

LS = least squares; SE = standard error
[a] p-value < 0.0001
[b] p-value < 0.001
[c] p-value < 0.05

Adolescents with atopic dermatitis

The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of ≥10%. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg dupilumab (two 200 mg injections) on day 1, followed by 200 mg once every other week (Q2W) for patients with baseline weight of <60 kg or an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg Q2W for patients with baseline weight of ≥ 60 kg; 2) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5% were White, 15.1% were Asian, and 12.0% were Black. At baseline 46.2% of patients had a baseline IGA score of 3 (moderate AD), 53.8% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5%, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean SCORing Atopic Dermatitis (SCORAD) score was 70.3, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.6. Overall, 92.0% of patients had at least one co-morbid allergic condition; 65.6% had allergic rhinitis, 53.6% had asthma, and 60.8% had food allergies. The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI), from baseline to week 16. Other evaluated outcomes included the proportion of subjects with EASI-50 or EASI-90 (improvement of at least 50% or 90% in EASI from baseline respectively), reduction in itch as measured by the peak pruritus NRS, and percent change in the SCORAD scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 10.

Table 10: Efficacy results of dupilumab in the adolescent atopic dermatitis study at Week 16 (FAS)

	AD-1526(FAS)[a]	
	Placebo	**Dupilumab 200 mg (<60 kg) and 300 mg (≥60 kg) Q2W**
Patients randomised	**85**[a]	**82**[a]
IGA 0 or 1[b], % responders[c]	2.4%	24.4%
EASI-50, % responders[c]	12.9%	61.0%
EASI-75, % responders[c]	8.2%	41.5%
EASI-90, % responders[c]	2.4%	23.2%
EASI, LS mean % change from baseline (+/-SE)	-23.6% (5.49)	-65.9% (3.99)
SCORAD, LS mean % change from baseline (+/- SE)	-17.6% (3.76)	-51.6% (3.23)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0% (4.09)	-47.9% (3.43)
Pruritus NRS (≥4-point improvement), % responders[c]	4.8%	36.6%
BSA LS mean % change from baseline (+/- SE)	-11.7% (2.72)	-30.1% (2.34)
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5 (0.50)
CDLQI, (≥6-point improvement), % responders	19.7%	60.6%
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1 (0.76)
POEM, (≥6-point improvement), % responders	9.5%	63.4%

[a] Full Analysis Set (FAS) includes all patients randomised.

[b] Responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.

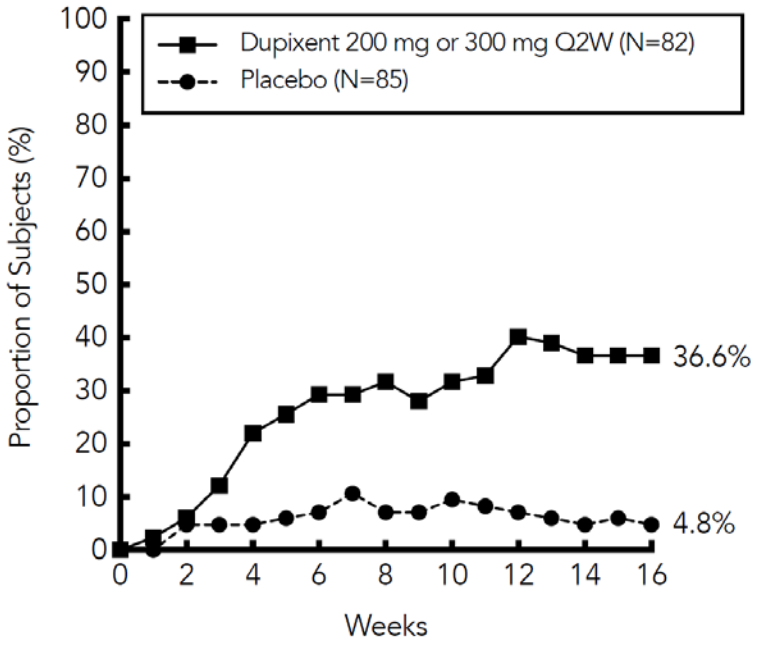
[c] Patients who received rescue treatment or with missing data were considered as non-responders (58.8% and 20.7% in the placebo and dupilumab arms, respectively).

All p–values <0.0001

A larger percentage of patients randomised to placebo needed rescue treatment (topical corticosteroids, systemic corticosteroids, or systemic non-steroidal immunosuppressants) as compared to the dupilumab group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 4; nominal p<0.001) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period (see Figure 5). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 5: Proportion of adolescent patients with ≥4-point improvement on the pruritus NRS in AD-1526 study[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomised.

The dupilumab group significantly improved patient-reported symptoms, the impact of AD on sleep and health-related quality of life as measured by POEM, SCORAD, and CDLQI scores at 16 weeks compared to placebo.

The long-term efficacy of dupilumab in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of dupilumab was assessed in open-label extension study (AD-1434). Efficacy data from this study suggests that clinical benefit provided at week 16 was sustained through week 52.

Clinical efficacy and safety in asthma

The asthma development program included three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older). Patients were enrolled without requiring a minimum baseline blood eosinophil or other type 2 inflammatory biomarker (e.g. FeNO or IgE) level. Asthma treatment guidelines define type 2 inflammation as eosinophilia ≥ 150 cells/mcL and/or FeNO ≥ 20 ppb. In DRI12544 and QUEST, the pre-specified subgroup analyses included blood eosinophils ≥ 150 and ≥ 300 cells/mcL, FeNO ≥ 25 and ≥ 50 ppb.

DRI12544 was a 24-week dose-ranging study which included 776 patients (18 years of age and older). Dupilumab compared with placebo was evaluated in adult patients with moderate to severe asthma on a medium-to-high dose inhaled corticosteroid and a long acting beta agonist. The primary endpoint was change from baseline to week 12 in FEV_1 (L). Annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period was also determined. Results were evaluated in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils count.

QUEST was a 52-week confirmatory study which included 1,902 patients (12 years of age and older). Dupilumab compared with placebo was evaluated in 107 adolescent and 1,795 adult patients with persistent asthma on a medium-to-high dose inhaled corticosteroid (ICS) and a second controller medication. Patients requiring a third controller were allowed to participate in this trial. Patients were

randomised to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent every other week (or matching placebo for either 200 mg (N = 317) or 300 mg (N= 321) every other week) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV_1 at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils and FeNO.

VENTURE was a 24-week oral corticosteroid-reduction study in 210 patients with asthma unrestricted by baseline type 2 biomarker levels who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, patients received 300 mg dupilumab (n=103) or placebo (n=107) once every other week for 24 weeks following an initial dose of 600 mg or placebo. Patients continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction in oral corticosteroid dose assessed in the overall population, based on a comparison of the oral corticosteroid dose at weeks 20 to 24 that maintained asthma control with the previously optimized (at baseline) oral corticosteroid dose.

The demographics and baseline characteristics of these 3 studies are provided in Table 11 below.

Table 11: Demographics and Baseline Characteristics of Asthma Trials

Parameter	**DRI12544 (n = 776)**	**QUEST (n = 1902)**	**VENTURE (n=210)**
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Duration of Asthma (years), mean ± SD	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)
Never smoked, (%)	77.4	80.7	80.5
Mean exacerbations in previous year ± SD	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use (%)[a]	49.5	51.5	88.6
Pre-dose FEV_1 (L) at baseline ± SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%)(± SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb ≥ 25 ≥ 50	 49.9 21.6	 49.6 20.5	 54.3 25.2
Mean total IgE IU/mL **(±** SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)

% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	77.8 41.9	71.4 43.7	71.4 42.4

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide; EOS = blood eosinophil
[a]The population in dupilumab asthma trials included patients on medium and high dose ICS. The medium ICS dose was defined as equal to 500 mcg fluticasone or equivalent per day.

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 12 and Table 13).

Table 12: Rate of Severe Exacerbations in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	**Baseline Blood EOS**							
	≥150 cells/mcL				**≥300 cells/mcL**			
	Exacerbations per Year			**% Reduction**	**Exacerbations per Year**			**% Reduction**
	N	**Rate (95% CI)**	**Rate Ratio (95%CI)**		**N**	**Rate (95% CI)**	**Rate Ratio (95%CI)**	
All Severe Exacerbations								
DRI12544 study								
Dupilumab 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28[a] (0.14, 0.55)	72%	65	0.30 (0.13, 0.68)	0.29[c] (0.11, 0.76)	71%
Dupilumab 300 mg Q2W	129	0.28 (0.16, 0.50)	0.27[b] (0.14, 0.52)	73%	64	0.20 (0.08, 0.52)	0.19[d] (0.07, 0.56)	81%
Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
QUEST study								
Dupilumab 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44[e] (0.34,0.58)	56%	264	0.37 (0.29, 0.48)	0.34[e] (0.24,0.48)	66%
Placebo	232	1.01 (0.81, 1.25)			148	1.08 (0.85, 1.38)		
Dupilumab 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 [e] (0.31,0.53)	60%	277	0.40 (0.32, 0.51)	0.33[e] (0.23,0.45)	67%
Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		

[a]p-value = 0.0003, [b]p-value = 0.0001, [c]p-value = 0.0116, [d]p-value = 0.0024, [e]p-value <0.0001

Table 13. Rate of Severe Exacerbations in QUEST Defined by Baseline FeNO Subgroups

Treatment	Exacerbations per Year			Percent Reduction
	N	Rate (95% CI)	Rate Ratio (95%CI)	
FeNO ≥ 25 ppb				
Dupilumab 200 mg Q2W	299	0.35 (0.27, 0.45)	0.35 (0.25, 0.50)[a]	65%
Placebo	162	1.00 (0.78, 1.30)		
Dupilumab 300 mg Q2W	310	0.43 (0.35, 0.54)	0.39 (0.28, 0.54) [a]	61%
Placebo	172	1.12 (0.88, 1.43)		
FeNO ≥ 50 ppb				
Dupilumab 200 mg Q2W	119	0.33 (0.22, 0.48)	0.31 (0.18, 0.52) [a]	69%
Placebo	71	1.057 (0.72, 1.55)		
Dupilumab 300 mg Q2W	124	0.39 (0.27, 0.558)	0.31 (0.19, 0.49) [a]	69%
Placebo	75	1.27 (0.90, 1.80)		

[a]p-value <0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalizations and/or emergency room visits due to severe exacerbations were reduced by 25.5% and 46.9% with dupilumab 200 mg or 300 mg every other week, respectively.

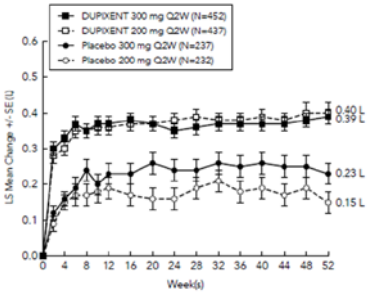
Lung Function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 14 and Table 15).

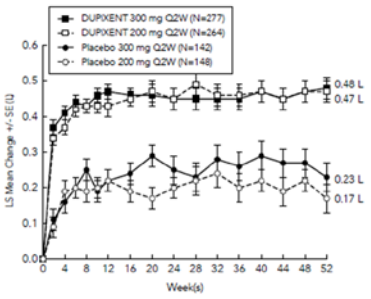
Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 6).

Figure 6: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time (Baseline Eosinophils ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb) in QUEST

QUEST: Blood Eosinophils ≥ 150 cells/mcL



QUEST: Blood Eosinophils ≥ 300 cells/mcL



QUEST: FeNO ≥ 25 ppb

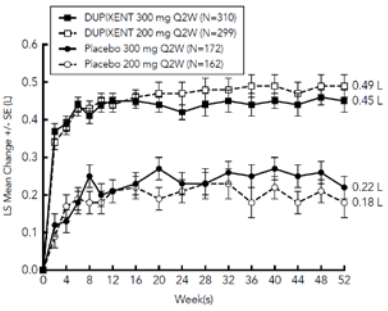


Table 14: Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 12 in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline Blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23[a] (0.13, 0.33)	65	0.43 (25.9)	0.26[c] (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18[b] (0.08, 0.27)	64	0.39 (25.8)	0.21[d] (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17[e] (0.11, 0.23)	264	0.43 (29.0)	0.21[e] (0.13, 0.29)
Placebo	232	0.18 (12.4)		148	0.21 (15.6)	
Dupilumab 300 mg Q2W	452	0.37 (25.3)	0.15[e] (0.09, 0.21)	277	0.47 (32.5)	0.24[e] (0.16, 0.32)
Placebo	237	0.22 (14.2)		142	0.22 (14.4)	

[a]p-value <0.0001, [b]p-value = 0.0004, [c]p-value = 0.0008, [d]p-value = 0.0063, [e]p-value <0.0001

Table 15: Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 12 and Week 52 in QUEST by Baseline FeNO Subgroups

Treatment		At Week 12		At Week 52	
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
FeNO ≥ 25 ppb					
Dupilumab 200 mg Q2W	288	0.44 (29.0%)	0.23 (0.15, 0.31)[a]	0.49 (31.6%)	0.30 (0.22, 0.39)[a]
Placebo	157	0.21 (14.1%)		0.18 (13.2%)	
Dupilumab 300 mg Q2W	295	0.45 (29.8%)	0.24 (0.16, 0.31)[a]	0.45 (30.5%)	0.23 (0.15, 0.31)[a]
Placebo	167	0.21 (13.7%)		0.22 (13.6%)	
FeNO ≥ 50 ppb					
Dupilumab 200 mg Q2W	114	0.53 (33.5%)	0.30 (0.17, 0.44)[a]	0.59 (36.4%)	0.38 (0.24, 0.53)[a]
Placebo	69	0.23 (14.9%)		0.21 (14.6%)	
Dupilumab 300 mg Q2W	113	0.59 (37.6%)	0.39 (0.26, 0.52)[a]	0.55 (35.8%)	0.30 (0.16, 0.44)[a]
Placebo	73	0.19 (13.0%)		0.25 (13.6%)	

[a]p-value < 0.0001

Quality of Life/Patient-Reported Outcomes in Asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE. The ACQ-5 and AQLQ(S) responder rate results in patients with elevated baseline biomarkers of type 2 inflammation in QUEST at week 52 are presented in Table 16.

Table 16: ACQ-5 and AQLQ(S) Responder Rates at Week 52 in QUEST

PRO	**Treatment**	**EOS ≥ 150 cells/mcL**		**EOS ≥ 300 cells/mcL**		**FeNO ≥ 25 ppb**	
		N	**Responder rate %**	**N**	**Responder rate (%)**	**N**	**Responder rate (%)**
ACQ-5	Dupilumab 200 mg Q2W	395	72.9	239	74.5	262	74.4
	Placebo	201	64.2	124	66.9	141	65.2
	Dupilumab 300 mg Q2W	408	70.1	248	71.0	277	75.8
	Placebo	217	64.5	129	64.3	159	64.2
AQLQ(S)	Dupilumab 200 mg Q2W	395	66.6	239	71.1	262	67.6
	Placebo	201	53.2	124	54.8	141	54.6
	Dupilumab 300 mg Q2W	408	62.0	248	64.5	277	65.3
	Placebo	217	53.9	129	55.0	159	58.5

Oral Corticosteroid Reduction Study (VENTURE)

VENTURE evaluated the effect of dupilumab on reducing the use of maintenance oral corticosteroids. Baseline characteristics are presented in Table 11. All patients were on oral corticosteroids for at least 6 months prior to the study initiation. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving dupilumab.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were reduced by 59% in subjects receiving dupilumab compared with those receiving placebo (annualized rate 0.65 and 1.60 for the dupilumab and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to week 24 was greater in subjects receiving dupilumab compared with those receiving placebo (LS mean difference for dupilumab versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function, on oral steroid and exacerbation reduction were similar irrespective of baseline levels of type 2 inflammatory biomarkers (e.g. blood eosinophils, FeNO). The ACQ-5 and AQLQ(S) were also assessed in VENTURE and showed improvements similar to those in QUEST.

The results for VENTURE by baseline biomarkers are presented in the Table 17.

Table 17: Effect of dupilumab on OCS dose reduction, VENTURE (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

	Baseline Blood EOS ≥ 150 cells/mcL		Baseline Blood EOS ≥ 300 cells/mcL		FeNO ≥ 25 ppb	
	Dupilumab 300 mg Q2W N=81	Placebo N=69	Dupilumab 300 mg Q2W N=48	Placebo N=41	Dupilumab 300 mg Q2W N=57	Placebo N=57
Primary endpoint (week 24)						
Percent reduction in OCS from baseline						
Mean overall percent reduction from baseline (%)	75.91	46.51	79.54	42.71	77.46	42.93
Difference (% [95% CI]) (Dupilumab vs. placebo)	29.39[b] (15.67, 43.12)		36.83[b] (18.94, 54.71)		34.53[b] (19.08, 49.97)	
Median % reduction in daily OCS dose from baseline	100	50	100	50	100	50
Percent reduction from baseline						
100%	54.3	33.3	60.4	31.7	52.6	28.1
≥ 90%	58.0	34.8	66.7	34.1	54.4	29.8
≥ 75%	72.8	44.9	77.1	41.5	73.7	36.8
≥ 50%	82.7	55.1	85.4	53.7	86.0	50.9
> 0%	87.7	66.7	85.4	63.4	89.5	66.7
No reduction or any increase in OCS dose, or dropped out of study	12.3	33.3	14.6	36.6	10.5	33.3
Secondary endpoint (week 24)[a]						
Proportion of patients achieving a reduction of OCS dose to <5 mg/day	77	44	84	40	79	34
Odds ratio (95% CI)	4.29[c] (2.04, 9.04)		8.04[d] (2.71, 23.82)		7.21[b] (2.69, 19.28)	

[a]Model estimates by logistic regression
[b]p-value <0.0001
[c]p-value =0.0001
[d]p-value =0.0002

Paediatric population

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in QUEST study and received either 200 mg (N=21) or 300 mg (N=18) dupilumab (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) every other week. Efficacy with respect to severe asthma exacerbations and lung function was observed in both adolescents and adults. For both the 200 mg and 300 mg every other week doses, significant improvements in FEV_1 (LS mean change from baseline at eek 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg every other week dose, patients had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in paediatric patients (< 12 years of age) with severe asthma have not been established. The adverse event profile in adolescents was generally similar to the adults.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of dupilumab is similar in patients with atopic dermatitis and asthma.

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 similar between AD and asthma patients, ranging between 61% and 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 ±SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 79.9±41.4 mcg/mL for 300 mg dose and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 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 9 weeks for the 200 mg Q2W, 10-11 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 1,472 patients with atopic dermatitis exposed to dupilumab 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 adult atopic dermatitis 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.

Of the 1,977 patients with asthma exposed to dupilumab, a total of 240 patients were 65 years or older and 39 patients were 75 years or older. Efficacy and safety in this age group were similar to the overall study population.

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 population
The pharmacokinetics of dupilumab in paediatric patients (< 12 years of age) with atopic dermatitis has not been studied.

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean ±SD steady state trough concentration of dupilumab was 54.5±27.0 mcg/ml.

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in QUEST study. The mean ±SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered every other week. No age-related pharmacokinetic difference was observed in adolescent patients after correction for body weight.

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-4Rα 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-4Rα, no fetal abnormalities were observed at dosages that saturate the IL-4Rα.

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-4Rα showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine hydrochloride
histidine
polysorbate 80
sodium acetate trihydrate
glacial 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

30 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.

<u>Dupixent 300 mg solution for injection in pre-filled syringe</u>

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 300 mg 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: 26 September 2017

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

▼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 200 mg solution for injection in pre-filled syringe
Dupixent 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dupilumab 200 mg solution for injection in pre-filled syringe

Each single-use pre-filled syringe contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

Dupilumab 200 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 200 mg of dupilumab in 1.14 ml solution (175 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

Atopic dermatitis

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents12 years and older who are candidates for systemic therapy.

Asthma

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated (see section 4.1).

Posology

Atopic Dermatitis

Adolescents
The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of dupilumab for subcutaneous administration in adolescent patients 12 years to 17 years of age with atopic dermatitis

Body Weight of Patient	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Adults
The recommended dose of dupilumab 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.

Dupilumab 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.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Asthma

The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is:
- An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). Steroid reductions should be accomplished gradually (see section 4.4).

Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Missed dose

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

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 for patients with asthma 12 years of age and older or in adults with atopic dermatitis (see section 5.2).

For patients 12 to 17 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (<60 kg) or 300 mg (≥60 kg).

Paediatric patients
The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established (see section 5.2). No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 12 years have not been established (see section 5.2). No data are available.

Method of administration

Subcutaneous use

Dupilumab 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 400 mg dose, two 200 mg injections should be administered consecutively in different injection sites.

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

A patient may self-inject dupilumab or the patient's caregiver may administer dupilumab 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 dupilumab 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

Dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus.

Systemic, topical, or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. This should be taken into consideration to determine type 2 status in patients taking oral corticosteroids (see section 5.1).

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 dupilumab should be discontinued immediately and appropriate therapy initiated. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program following the administration of dupilumab. Anaphylactic reaction has been reported very rarely in the asthma development program following the administration of dupilumab (section 4.8).

Eosinophilic conditions

Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with dupilumab in adult patients who participated in the asthma development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy.

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. Dupilumab 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 dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection resolves.

Conjunctivitis related events

Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (section 4.8).

Atopic dermatitis patients with comorbid asthma

Patients on dupilumab for moderate-to-severe atopic dermatitis who also have 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 dupilumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed, see section 4.5. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

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 dupilumab may receive concurrent inactivated or non-live vaccinations. For information on live vaccines see section 4.4.

In a clinical study of AD patients, the effects of dupilumab on the pharmacokinetics (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.

An effect of dupilumab on the PK of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on dupilumab pharmacokinetics on patients with moderate to severe asthma.

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). Dupilumab 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 dupilumab 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

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

4.8 Undesirable effects

Atopic dermatitis

Adults with atopic dermatitis

Summary of the safety profile

The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Very rare cases of serum sickness/serum sickness-like reactions have been reported in the atopic dermatitis development program (see section 4.4).

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 dupilumab 300 mg Q2W group, 1.5 % of the dupilumab 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 dupilumab 300 mg Q2W + TCS group, and 2.9 % of the dupilumab 300 mg QW + TCS group.

Tabulated list of adverse reactions

The safety of dupilumab 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, 1,689 subjects were treated with subcutaneous injections of dupilumab, with or without concomitant topical corticosteroids (TCS). A total of 305 patients were treated with dupilumab for at least 1 year.

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: List of adverse reactions in atopic dermatitis

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

Adolescents with atopic dermatitis

The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of dupilumab in these patients followed through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of dupilumab was assessed in an open-label extension study in patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of dupilumab in patients followed through week 52 was similar to the safety profile observed at week 16 in AD-1526 study. The long-term safety profile of dupilumab observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

Summary of the safety profile

The most common adverse reaction was injection site erythema. Anaphylactic reaction has been reported very rarely in the asthma development program (see section 4.4).

In DRI12544 and QUEST studies, the proportion of patients who discontinued treatment due to adverse events was 4.3% of the placebo group, 3.2% of the dupilumab 200 mg Q2W group, and 6.1% of the dupilumab 300 mg Q2W group.

Tabulated list of adverse reactions

A total of 2,888 adult and adolescent patients with moderate-to-severe asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). Of these, 2,678 had a history of 1 or more severe exacerbations in the year prior to enrolment despite regular use of medium-to-high dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 patients with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE).

Listed in Table 3 are adverse reactions observed in asthma clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: List of adverse reactions in asthma

MedDRA System Organ Class	**Frequency**	**Adverse Reaction**
Immune system disorders	Very rare	Anaphylactic reaction
General disorders and administration site conditions	Very common Common Common Common	Injection site erythema Injection site oedema Injection site pain Injection site pruritus

Description of selected adverse reactions in atopic dermatitis and asthma indications

Hypersensitivity
Very rare cases of serum sickness/serum sickness-like reactions and anaphylactic reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and related events
Conjunctivitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis recovered or were recovering during the treatment period. Among asthma patients frequency of conjunctivitis was low and similar between dupilumab and placebo (see section 4.4).

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

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophil counts declined to near baseline levels during study treatment.

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 2 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients.

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

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

Anti-Drug-Antibodies (ADA) responses were not generally associated with impact on dupilumab exposure, safety, or efficacy.

Approximately 6 % of patients with atopic dermatitis or asthma who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies.

Approximately 9 % of patients with asthma who received dupilumab 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4 % exhibited persistent ADA responses and approximately 4 % had neutralizing antibodies.

Approximately 5 % of patients in the placebo groups in the 52 week studies were also positive for antibodies to dupilumab; approximately 2 % exhibited persistent ADA response and approximately 1% had neutralizing antibodies.

Less than 0.4 % 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).

Paediatric population

The safety profile observed in the adolescents aged 12 to 17 years in atopic dermatitis clinical trials was similar to that seen in adults.

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in the 52 week QUEST study. The safety profile observed was similar to that seen in adults.

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 dupilumab 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: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH05

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-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis and asthma. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.

Pharmacodynamic effects

In atopic dermatitis 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 dupilumab treatment.

In asthma clinical trials, dupilumab treatment markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin in asthma subjects relative to placebo. These reductions in type 2 inflammatory biomarkers were comparable for the 200 mg Q2W and 300 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Clinical efficacy and safety in atopic dermatitis

Adolescents with atopic dermatitis

The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (AD-1526) in 251 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of ≥10%. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received 1) an initial dose of 400 mg dupilumab (two 200 mg injections) on day 1, followed by 200 mg once every other week (Q2W) for patients with baseline weight of <60 kg or an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg Q2W for patients with baseline weight of ≥ 60 kg; 2) an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg every 4 weeks (Q4W) regardless of baseline body weight; or 3) matching placebo. Dupilumab was administered by subcutaneous (SC) injection. If needed to control intolerable symptoms, patients were permitted to receive rescue treatment at the discretion of the investigator. Patients who received rescue treatment were considered non-responders.

In this study, the mean age was 14.5 years, the median weight was 59.4 kg, 41.0 % were female, 62.5% were White, 15.1% were Asian, and 12.0% were Black. At baseline 46.2% of patients had a baseline IGA score of 3 (moderate AD), 53.8% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 56.5%, and 42.4 % of patients had received prior systemic immunosuppressants. Also at baseline the mean Eczema Area and Severity Index (EASI) score was 35.5, the baseline weekly averaged pruritus Numerical Rating Scale (NRS) was 7.6, the baseline mean SCORing Atopic Dermatitis (SCORAD) score was 70.3, the baseline mean Patient Oriented Eczema Measure (POEM) score was 21.0, and the baseline mean Children Dermatology

Life Quality Index (CDLQI) was 13.6. Overall, 92.0% of patients had at least one co-morbid allergic condition; 65.6% had allergic rhinitis, 53.6% had asthma, and 60.8% had food allergies. The co-primary endpoint was the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") least a 2-point improvement and the proportion of patients with EASI-75 (improvement of at least 75% in EASI), from baseline to week 16. Other evaluated outcomes included the proportion of subjects with EASI-50 or EASI-90 (improvement of at least 50% or 90% in EASI from baseline respectively), reduction in itch as measured by the peak pruritus NRS, and percent change in the SCORAD scale from baseline to week 16. Additional secondary endpoints included mean change from baseline to week 16 in the POEM and CDLQI scores.

Clinical Response

The efficacy results at week 16 for adolescent atopic dermatitis study are presented in Table 4.

Table 4: Efficacy results of dupilumab in the adolescent atopic dermatitis study at Week 16 (FAS)

	AD-1526(FAS)[a]	
	Placebo	**Dupilumab 200 mg (<60 kg) and 300 mg (≥60 kg) Q2W**
Patients randomised	**85**[a]	**82**[a]
IGA 0 or 1[b], % responders[c]	2.4%	24.4%
EASI-50, % responders[c]	12.9%	61.0%
EASI-75, % responders[c]	8.2%	41.5%
EASI-90, % responders[c]	2.4%	23.2%
EASI, LS mean % change from baseline (+/-SE)	-23.6% (5.49)	-65.9% (3.99)
SCORAD, LS mean % change from baseline (+/- SE)	-17.6% (3.76)	-51.6% (3.23)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-19.0% (4.09)	-47.9% (3.43)
Pruritus NRS (≥4-point improvement), % responders[c]	4.8%	36.6%
BSA LS mean % change from baseline (+/- SE)	-11.7% (2.72)	-30.1% (2.34)
CDLQI, LS mean change from baseline (+/-SE)	-5.1 (0.62)	-8.5 (0.50)
CDLQI, (≥6-point improvement), % responders	19.7%	60.6%
POEM, LS mean change from baseline (+/- SE)	-3.8 (0.96)	-10.1 (0.76)
POEM, (≥6-point improvement), % responders	9.5%	63.4%

[a] Full Analysis Set (FAS) includes all patients randomised.

[b] Responder was defined as a subject 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 (58.8% and 20.7% in the placebo and dupilumab arms, respectively).

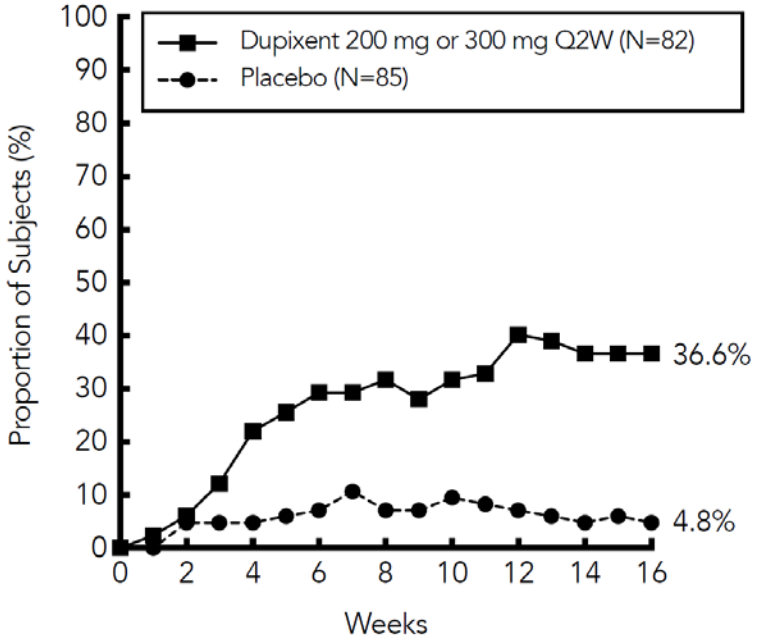
All p –values <0.0001

A larger percentage of patients randomised to placebo needed rescue treatment (topical corticosteroids, systemic corticosteroids, or systemic non-steroidal immunosuppressants) as compared to the dupilumab group (58.8% and 20.7%, respectively).

A significantly greater proportion of patients randomised to dupilumab achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 4; nominal p<0.001) and the proportion of patients responding on the pruritus NRS continued to increase

through the treatment period (see Figure 1). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.

Figure 1: Proportion of adolescent patients with ≥4-point improvement on the pruritus NRS in AD-1526 study[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomised.

The dupilumab group significantly improved patient-reported symptoms, the impact of AD on sleep and health-related quality of life as measured by POEM, SCORAD, and CDLQI scores at 16 weeks compared to placebo.

The long-term efficacy of dupilumab in adolescent patients with moderate-to-severe AD who had participated in previous clinical trials of dupilumab was assessed in open-label extension study (AD-1434). Efficacy data from this study suggests that clinical benefit provided at week 16 was sustained through week 52.

Adults with atopic dermatitis

For clinical data in adults with atopic dermatitis please refer to the dupilumab 300 mg Summary of Product Characteristics.

Clinical efficacy and safety in asthma

The asthma development program included three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older). Patients were enrolled without requiring a minimum baseline blood eosinophil or other type 2 inflammatory biomarkers (e.g. FeNO or IgE) level. Asthma treatment guidelines define type 2 inflammation as eosinophilia ≥ 150 cells/mcL and/or FeNO ≥ 20 ppb. In DRI12544 and QUEST, the pre-specified subgroup analyses included blood eosinophils ≥ 150 and ≥ 300 cells/mcL, FeNO ≥ 25 and ≥ 50 ppb.

DRI12544 was a 24-week dose-ranging study which included 776 patients (18 years of age and older). Dupilumab compared with placebo was evaluated in adult patients with moderate to severe asthma on a medium-to-high dose inhaled corticosteroid and a long acting beta agonist. The primary endpoint was change from baseline to week 12 in FEV_1 (L). Annualized rate of severe asthma exacerbation

events during the 24-week placebo controlled treatment period was also determined. Results were evaluated in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophil count.

QUEST was a 52-week confirmatory study which included 1,902 patients (12 years of age and older). Dupilumab compared with placebo was evaluated in 107 adolescent and 1,795 adult patients with persistent asthma on a medium-to-high dose inhaled corticosteroid (ICS) and a second controller medication. Patients requiring a third controller were allowed to participate in this trial. Patients were randomised to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent every other week (or matching placebo for either 200 mg (N = 317) or 300 mg (N= 321) every other week) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV_1 at week 12 in the overall population (unrestricted by minimum baseline eosinophils or other type 2 inflammatory biomarkers) and subgroups based on baseline blood eosinophils count and FeNO.

VENTURE was a 24-week oral corticosteroid-reduction study in 210 patients with asthma unrestricted by baseline type 2 biomarker levels who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, patients received 300 mg dupilumab (n=103) or placebo (n=107) once every other week for 24 weeks following an initial dose of 600 mg or placebo. Patients continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction in oral corticosteroid dose assessed in the overall population, based on a comparison of the oral corticosteroid dose at weeks 20 to 24 that maintained asthma control with the previously optimized (at baseline) oral corticosteroid dose.

The demographics and baseline characteristics of these 3 studies are provided in Table 5 below.

Table 5: Demographics and Baseline Characteristics of Asthma Trials

Parameter	DRI12544 (n = 776)	QUEST (n = 1902)	VENTURE (n=210)
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Duration of Asthma (years), mean ± SD	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)
Never smoked, (%)	77.4	80.7	80.5
Mean exacerbations in previous year ± SD	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use (%)[a]	49.5	51.5	88.6
Pre-dose FEV_1 (L) at baseline ± SD	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%)(± SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb ≥ 25 ≥ 50	 49.9 21.6	 49.6 20.5	 54.3 25.2
Mean total IgE IU/mL (± SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 77.8 41.9	 71.4 43.7	 71.4 42.4

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide; EOS = blood eosinophil

[a]The population in dupilumab asthma trials included patients on medium and high dose ICS. The medium ICS dose was defined as equal to 500 mcg fluticasone or equivalent per day.

Exacerbations

In the overall population in DRI12544 and QUEST subjects receiving either dupilumab 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo. There were greater reductions in exacerbations in subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 6 and Table 7).

Table 6: Rate of Severe Exacerbations in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline Blood EOS							
	≥150 cells/mcL				≥300 cells/mcL			
	Exacerbations per Year			% Reduction	Exacerbations per Year			% Reduction
	N	Rate (95% CI)	Rate Ratio (95%CI)		N	Rate (95% CI)	Rate Ratio (95%CI)	
All Severe Exacerbations								
DRI12544 study								
Dupilumab 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28[a] (0.14, 0.55)	72%	65	0.30 (0.13, 0.68)	0.29[c] (0.11, 0.76)	71%
Dupilumab 300 mg Q2W	129	0.28 (0.16, 0.50)	0.27[b] (0.14, 0.52)	73%	64	0.20 (0.08, 0.52)	0.19[d] (0.07, 0.56)	81%
Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
QUEST study								
Dupilumab 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44[e] (0.34,0.58)	56%	264	0.37 (0.29, 0.48)	0.34[e] (0.24,0.48)	66%
Placebo	232	1.01 (0.81, 1.25)			148	1.08 (0.85, 1.38)		
Dupilumab 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 [e] (0.31,0.53)	60%	277	0.40 (0.32, 0.51)	0.33[e] (0.23,0.45)	67%
Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		

[a]p-value = 0.0003, [b]p-value = 0.0001, [c]p-value = 0.0116, [d]p-value = 0.0024, [e]p-value <0.0001

Table 7: **Rate of Severe Exacerbations in QUEST Defined by Baseline FeNO Subgroups**

Treatment	Exacerbations per Year			Percent Reduction
	N	Rate (95% CI)	Rate Ratio (95%CI)	
FeNO ≥ 25 ppb				
Dupilumab 200 mg Q2W	299	0.35 (0.27, 0.45)	0.35 (0.25, 0.50)[a]	65%
Placebo	162	1.00 (0.78, 1.30)		
Dupilumab 300 mg Q2W	310	0.43 (0.35, 0.54)	0.39 (0.28, 0.54) [a]	61%
Placebo	172	1.12 (0.88, 1.43)		
FeNO ≥ 50 ppb				
Dupilumab 200 mg Q2W	119	0.33 (0.22, 0.48)	0.31 (0.18, 0.52) [a]	69%
Placebo	71	1.057 (0.72, 1.55)		
Dupilumab 300 mg Q2W	124	0.39 (0.27, 0.558)	0.31 (0.19, 0.49) [a]	69%
Placebo	75	1.27 (0.90, 1.80)		

[a]p-value <0.0001

In the pooled analysis of DRI12544 and QUEST, hospitalizations and/or emergency room visits due to severe exacerbations were reduced by 25.5% and 46.9% with dupilumab 200 mg or 300 mg every other week, respectively.

Lung Function

Clinically significant increases in pre-bronchodilator FEV_1 were observed at week 12 for DRI12544 and QUEST. There were greater improvements in FEV_1 in the subjects with higher baseline levels of type 2 inflammatory biomarkers such as blood eosinophils or FeNO (Table 8 and Table 9).

Significant improvements in FEV_1 were observed as early as week 2 following the first dose of dupilumab for both the 200 mg and 300 mg dose strengths and were maintained through week 24 (DRI12544) and week 52 in QUEST (see Figure 2).

Figure 2: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time (Baseline Eosinophils ≥ 150 and ≥ 300 cells/mcL and FeNO ≥25 ppb) in QUEST

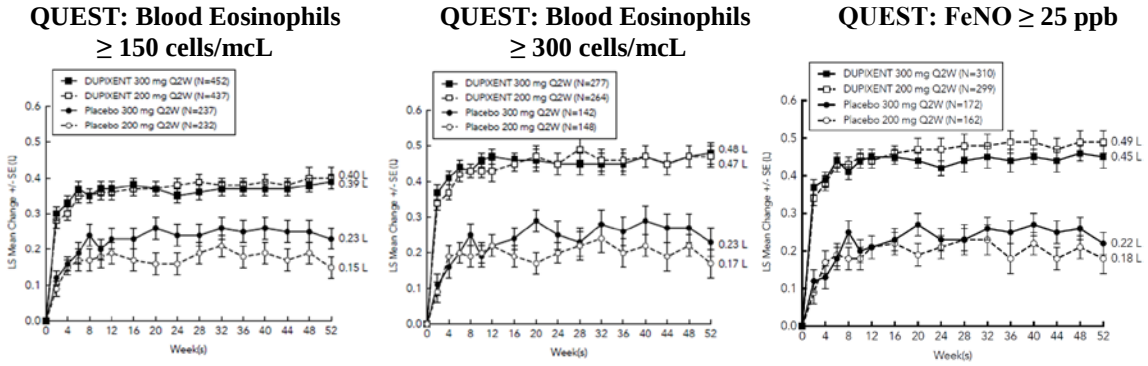


Table 8: Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 12 in DRI12544 and QUEST (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL)

Treatment	Baseline Blood EOS					
	≥ 150 cells/mcL			≥ 300 cells/mcL		
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544 study						
Dupilumab 200 mg Q2W	120	0.32 (18.25)	0.23[a] (0.13, 0.33)	65	0.43 (25.9)	0.26[c] (0.11, 0.40)
Dupilumab 300 mg Q2W	129	0.26 (17.1)	0.18[b] (0.08, 0.27)	64	0.39 (25.8)	0.21[d] (0.06, 0.36)
Placebo	127	0.09 (4.36)		68	0.18 (10.2)	
QUEST study						
Dupilumab 200 mg Q2W	437	0.36 (23.6)	0.17[e] (0.11, 0.23)	264	0.43 (29.0)	0.21[e] (0.13, 0.29)
Placebo	232	0.18 (12.4)		148	0.21 (15.6)	
Dupilumab 300 mg Q2W	452	0.37 (25.3)	0.15[e] (0.09, 0.21)	277	0.47 (32.5)	0.24[e] (0.16, 0.32)
Placebo	237	0.22 (14.2)		142	0.22 (14.4)	

[a]p-value <0.0001, [b]p-value = 0.0004, [c]p-value = 0.0008, [d]p-value = 0.0063, [e]p-value <0.0001

Table 9: Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 12 and Week 52 in QUEST by Baseline FeNO Subgroups

Treatment		At Week 12		At Week 52	
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
FeNO ≥ 25 ppb					
Dupilumab 200 mg Q2W	288	0.44 (29.0%)	0.23 (0.15, 0.31)[a]	0.49 (31.6%)	0.30 (0.22, 0.39)[a]
Placebo	157	0.21 (14.1%)		0.18 (13.2%)	
Dupilumab 300 mg Q2W	295	0.45 (29.8%)	0.24 (0.16, 0.31)[a]	0.45 (30.5%)	0.23 (0.15, 0.31)[a]
Placebo	167	0.21 (13.7%)		0.22 (13.6%)	
FeNO ≥ 50 ppb					
Dupilumab 200 mg Q2W	114	0.53 (33.5%)	0.30 (0.17, 0.44)[a]	0.59 (36.4%)	0.38 (0.24, 0.53)[a]
Placebo	69	0.23 (14.9%)		0.21 (14.6%)	
Dupilumab 300 mg Q2W	113	0.59 (37.6%)	0.39 (0.26, 0.52)[a]	0.55 (35.8%)	0.30 (0.16, 0.44)[a]
Placebo	73	0.19 (13.0%)		0.25 (13.6%)	

[a]p-value < 0.0001

Quality of Life/Patient-Reported Outcomes in Asthma

Pre-specified secondary endpoint of ACQ-5 and AQLQ(S) responder rates were analysed at 24 weeks (DRI12544 and VENTURE) and at 52 weeks (QUEST). The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)). Improvements in ACQ-5 and AQLQ(S) were observed as early as week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study. Similar results were observed in VENTURE. The ACQ-5 and AQLQ(S) responder rate results in patients with elevated baseline biomarkers of type 2 inflammation in QUEST at week 52 are presented in Table 10.

Table 10: ACQ-5 and AQLQ(S) Responder Rates at Week 52 in QUEST

PRO	Treatment	EOS ≥150 cells/mcL		EOS ≥300 cells/mcL		FeNO ≥25 ppb	
		N	Responder rate %	N	Responder rate (%)	N	Responder rate (%)
ACQ-5	Dupilumab 200 mg Q2W	395	72.9	239	74.5	262	74.4
	Placebo	201	64.2	124	66.9	141	65.2
	Dupilumab 300 mg Q2W	408	70.1	248	71.0	277	75.8
	Placebo	217	64.5	129	64.3	159	64.2
AQLQ(S)	Dupilumab 200 mg Q2W	395	66.6	239	71.1	262	67.6
	Placebo	201	53.2	124	54.8	141	54.6
	Dupilumab 300 mg Q2W	408	62.0	248	64.5	277	65.3
	Placebo	217	53.9	129	55.0	159	58.5

Oral Corticosteroid Reduction Study (VENTURE)

VENTURE evaluated the effect of dupilumab on reducing the use of maintenance oral corticosteroids. Baseline characteristics are presented in Table 5. All patients were on oral corticosteroids for at least 6 months prior to the study initiation. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving dupilumab.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were reduced by 59% in subjects receiving dupilumab compared with those receiving placebo (annualized rate 0.65 and 1.60 for the dupilumab and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to week 24 was greater in subjects receiving dupilumab compared with those receiving placebo (LS mean difference for dupilumab versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function, on oral steroid and exacerbation reduction were similar irrespective of baseline levels of type 2 inflammatory biomarkers (e.g. blood eosinophils, FeNO). The ACQ-5 and AQLQ(S) were also assessed in VENTURE and showed improvements similar to those in QUEST.

The results for VENTURE by baseline biomarkers are presented in the Table 11.

Table 11: Effect of dupilumab on OCS dose reduction, VENTURE (Baseline Blood Eosinophil Levels ≥ 150 and ≥ 300 cells/mcL and FeNO ≥ 25 ppb)

	Baseline Blood EOS ≥ 150 cells/mcL		**Baseline Blood EOS ≥ 300 cells/mcL**		**FeNO ≥ 25 ppb**	
	Dupilumab 300 mg Q2W N=81	**Placebo N=69**	**Dupilumab 300 mg Q2W N=48**	**Placebo N=41**	**Dupilumab 300 mg Q2W N=57**	**Placebo N=57**
Primary endpoint (week 24)						
Percent reduction in OCS from baseline						
Mean overall percent reduction from baseline (%)	75.91	46.51	79.54	42.71	77.46	42.93
Difference (% [95% CI]) (Dupilumab vs. placebo)	29.39[b] (15.67, 43.12)		36.83[b] (18.94, 54.71)		34.53[b] (19.08, 49.97)	
Median % reduction in daily OCS dose from baseline	100	50	100	50	100	50
Percent reduction from baseline						
100%	54.3	33.3	60.4	31.7	52.6	28.1
≥ 90%	58.0	34.8	66.7	34.1	54.4	29.8
≥ 75%	72.8	44.9	77.1	41.5	73.7	36.8
≥ 50%	82.7	55.1	85.4	53.7	86.0	50.9
> 0%	87.7	66.7	85.4	63.4	89.5	66.7
No reduction or any increase in OCS dose, or dropped out of study	12.3	33.3	14.6	36.6	10.5	33.3
Secondary endpoint (week 24)[a]						
Proportion of patients achieving a reduction of OCS dose to <5 mg/day	77	44	84	40	79	34
Odds ratio (95% CI)	4.29[c] (2.04, 9.04)		8.04[d] (2.71, 23.82)		7.21[b] (2.69, 19.28)	

[a]Model estimates by logistic regression
[b]p-value <0.0001
[c]p-value =0.0001
[d]p-value =0.0002

Paediatric population

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in QUEST study and received either 200 mg (N=21) or 300 mg (N=18) dupilumab (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) every other week. Efficacy with respect to severe asthma exacerbations and lung function was observed in both adolescents and adults. For both the 200 mg and 300 mg every other week doses, significant improvements in FEV_1 (LS mean change from baseline at eek 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg every other week dose, patients had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in paediatric patients (< 12 years of age) with severe asthma have not been established. The adverse event profile in adolescents was generally similar to the adults.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of dupilumab is similar in patients with atopic dermatitis and asthma.

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 similar between AD and asthma patients, ranging between 61% and 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 ±SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 79.9±41.4 mcg/mL for 300 mg dose and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 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 9 weeks for the 200 mg Q2W, 10-11 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 1,472 patients with atopic dermatitis exposed to dupilumab 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 adult atopic dermatitis 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.

Of the 1,977 patients with asthma exposed to dupilumab, a total of 240 patients were 65 years or older and 39 patients were 75 years or older. Efficacy and safety in this age group were similar to the overall study population.

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 population
The pharmacokinetics of dupilumab in paediatric patients (< 12 years of age) with atopic dermatitis has not been studied.

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean ±SD steady state trough concentration of dupilumab was 54.5±27.0 mcg/ml.

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in QUEST study. The mean ±SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL,

respectively, for 300 mg or 200 mg administered every other week. No age-related pharmacokinetic difference was observed in adolescent patients after correction for body weight.

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-4Rα 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-4Rα, no fetal abnormalities were observed at dosages that saturate the IL-4Rα.

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-4Rα showed no impairment of fertility (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine hydrochloride
histidine
polysorbate 80
sodium acetate trihydrate
glacial 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

18 months.

If necessary, pre-filled syringes or pre-filled pens 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

1.14 ml solution in a siliconised type-1 clear glass pre-filled syringe with needle shield or pre-filled pen, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

Dupixent 200 mg solution for injection in pre-filled syringe

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

Dupixent 200 mg solution for injection in pre-filled pen

Pack size:
- 1 pre-filled pen
- 2 pre-filled pens
- 3 pre-filled pens
- 6 pre-filled pens

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 or in a pre-filled pen 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 200 mg pre-filled syringe or pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting for 30 min before injecting Dupixent.

The pre-filled syringe or the pre-filled pen 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 or the pre-filled pen 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/1/17/1229/009
EU/1/17/1229/010

EU/1/17/1229/011
EU/1/17/1229/012
EU/1/17/1229/013
EU/1/17/1229/014
EU/1/17/1229/015
EU/1/17/1229/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2017

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

Regeneron Ireland Unlimited Company (U.C.)
Ballycummin
Raheen Business Park
Limerick
Ireland

Genzyme Flanders BVBA
Cipalstraat 8,
B-2440 Geel
Belgium

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 syringe

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 syringe

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 syringe

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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

Read the package leaflet before use.
For single use only
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 syringe

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 syringe

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: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 syringe

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-filled syringe with needle shield 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 200 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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

Read the package leaflet before use.
For single use only
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/1/17/1229/009 1 pre-filled syringe with needle shield
EU/1/17/1229/010 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 200 mg syringe

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 200 mg - Multipack (contains Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 200 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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

Read the package leaflet before use.
For single use only
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/1/17/1229/011 3 pre-filled syringes with needle shield (3 packs of 1)
EU/1/17/1229/012 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 200 mg syringe

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 200 mg - Multipack (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 200 mg solution for injection in pre-filled syringe
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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

Read the package leaflet before use.
For single use only
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/1/17/1229/011 3 pre-filled syringes with needle shield (3 packs of 1)
EU/1/17/1229/012 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 200 mg syringe

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 200 mg

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

Dupixent 200 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

200 mg/1.14 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON
Pre-filled pen 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Dupixent 200 mg solution for injection in pre-filled pen
dupilumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 200 mg of dupilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
2 pre-filled pens
3 pre-filled pens
6 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only
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/1/17/1229/013 1 pre-filled pen
EU/1/17/1229/014 2 pre-filled pens
EU/1/17/1229/015 3 pre-filled pens
EU/1/17/1229/016 6 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dupixent 200 mg 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

LABEL
Pre-filled pen 200 mg

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

Dupixent 200 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

200 mg/1.14 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

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 and asthma.

Dupixent is used to treat adults and adolescents 12 years and older 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.

Dupixent is also used with other asthma medicines for the maintenance treatment of severe asthma in adults and adolescents (12 years of age and older) whose asthma is not controlled with their current asthma medicines. Dupixent helps prevent severe asthma attacks (exacerbations) and can improve your breathing. Dupixent may also help reduce the amount of another group of medicines you need to control your asthma, called oral corticosteroids, while preventing severe asthma attacks and improving your breathing.

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:

Dupixent is not a rescue medicine and should not be used to treat a sudden asthma attack.

Allergic reactions
Very rarely, Dupixent can cause serious side effects, including allergic (hypersensitivity) reactions and anaphylactic reaction. You must look out for signs of these conditions (i.e. breathing problems, swelling of the face, mouth, and tongue, fainting, dizziness, feeling lightheaded (low blood pressure), 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.

Eosinophilic conditions
Rarely patients taking an asthma medicine may develop inflammation of blood vessels or lungs due to an increase of certain white blood cells (eosinophilia). It is not known whether this is caused by Dupixent. This usually, but not always, happens in people who also take a steroid medicine which is being stopped or for which the dose is being lowered. Tell your doctor immediately if you develop a combination of symptoms such as a flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash.

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 or if your asthma remains uncontrolled or worsens during treatment with this medicine.

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

Children and adolescents

The safety and benefits of Dupixent are not yet known in children and adolescents with atopic dermatitis below the age of 12.

The safety and benefits of Dupixent are not yet known in children with asthma below the age of 12.

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.

Do not stop or reduce your asthma medicines, unless instructed by your doctor. These medicines (especially ones called *corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Dupixent.

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.

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).

Recommended dose in adults with atopic dermatitis
In atopic dermatitis, the recommended first dose is 600 mg (two 300 mg injections), followed by 300 mg given every two weeks by subcutaneous injection.

Recommended dose in adolescents with atopic dermatitis
The recommended dose of Dupixent for adolescents (12 to 17 years of age) with atopic dermatitis is based on body weight:

Body Weight of Patient	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Recommended dose in adult and adolescent patients with asthma
For asthma, the recommended dose of Dupixent for adult and adolescents patients (12 years of age and older) is:

- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.
- For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as subcutaneous injection.

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.

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, including anaphylactic reaction; the signs of allergic reaction or anaphylactic reaction may include:
- breathing problems
- swelling of the face, mouth, and tongue
- fainting, dizziness, feeling lightheaded (low blood pressure)
- 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.

<u>Other side effects</u>

Very Common (may affect more than 1 in 10 people) atopic dermatitis and asthma:
- injection site reactions (i.e. redness, swelling, and itching)

Common (may affect up to 1 in 10 people) atopic dermatitis only:
- 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 arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 as 300 mg pre-filled syringes 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
sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

Manufacturer
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1051 Boulevard Industriel,
76580 LE TRAIT,
FRANCE

Sanofi-Aventis Deutschland GmbH

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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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Vistor hf.

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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

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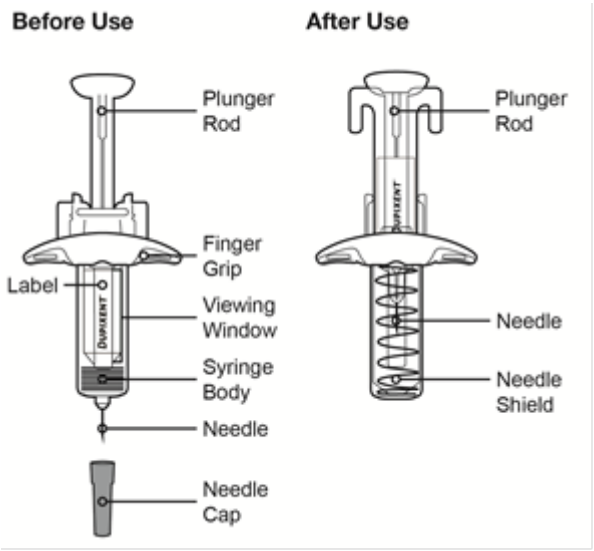
Dupixent 300 mg solution for injection in a pre-filled syringe with needle shield
dupilumab

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. In adolescents 12 years and older, it is recommended that Dupixent be administered by or under supervision of an adult.

- 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 2ºC and 8ºC.
- **Do not** keep Dupixent at room temperature (< 25ºC) 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.

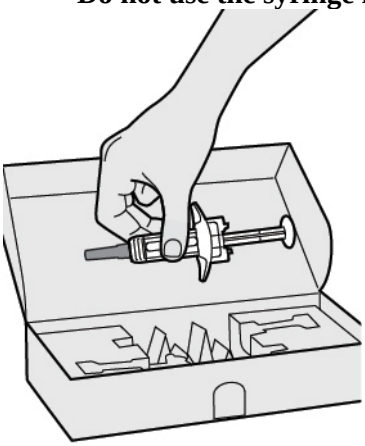
- **Do not** shake the syringe at any time.
- **Do not** heat the syringe.
- **Do not** freeze the syringe.
- **Do not** place the syringe into direct sunlight.

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 dropped on a hard surface or damaged.



Step 2: Prepare

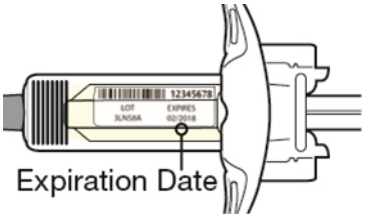
Ensure you have the following:
- the Dupixent pre-filled syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 12)

**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.



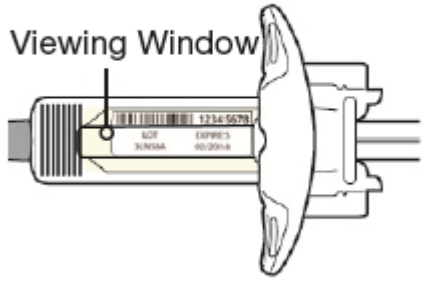
Step 3: Inspect

Look at the medicine 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.**



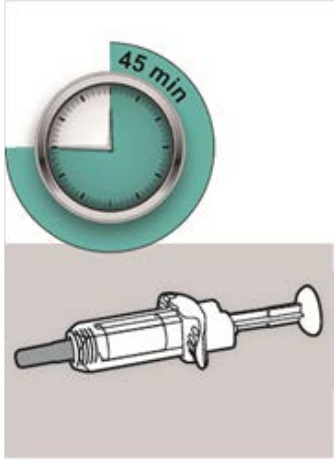
Step 4: Wait 45 minutes

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.**

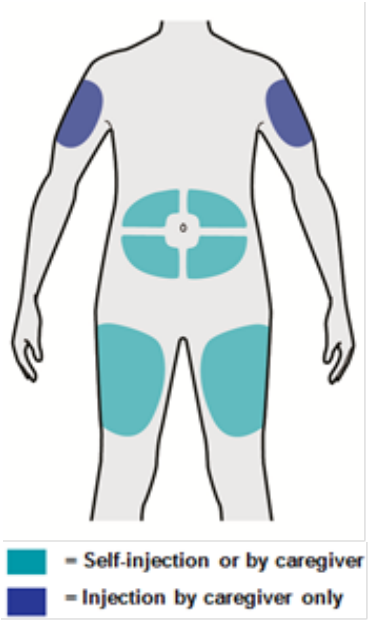


Step 5: Choose

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.**



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.**

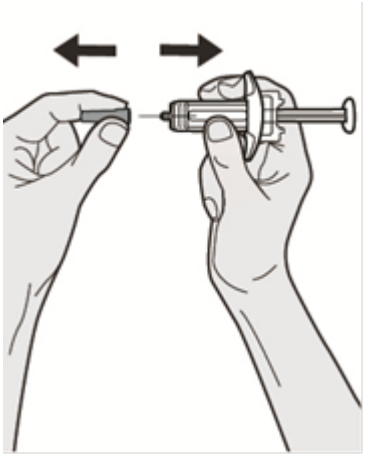
Step 7: Pull

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.**

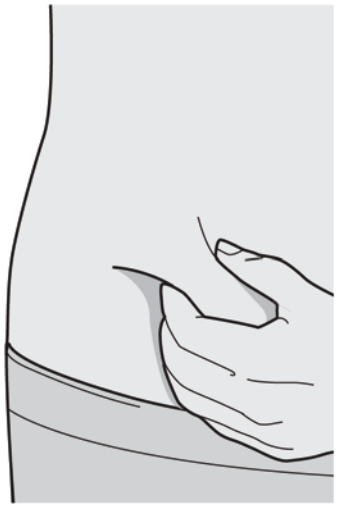
Do not touch the needle.

Inject your medicine immediately after removing the needle cap.



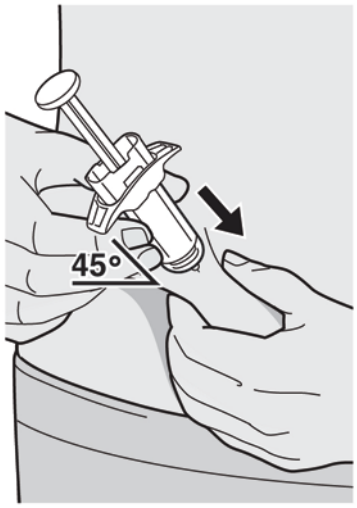
Step 8: Pinch

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 45º 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.

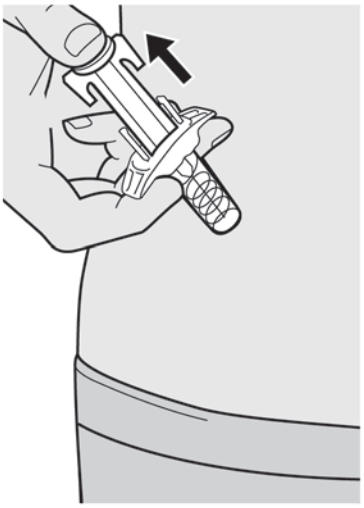
Note: You will feel some resistance. This is normal.

Step 11: Release and Remove

Lift your thumb to release the plunger rod until the needle is covered by the needle shield and then remove the syringe from the injection site.
Lightly press a cotton ball or gauze on the injection site if you see any blood.

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

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

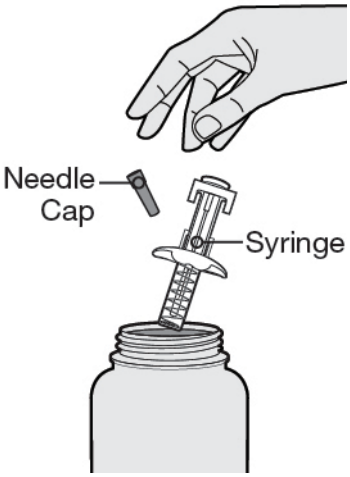


Step 12: Dispose

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

Do not put the needle cap back on.

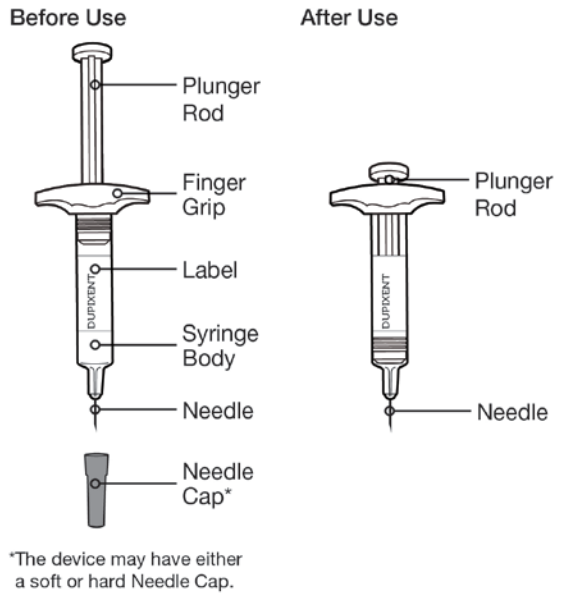
Always keep the container out of the reach of children.



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.



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- 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.
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- **Do not** get rid of any air bubbles in the syringe.
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- **Do not** shake the syringe at any time.
- **Do not** heat the syringe.
- **Do not** freeze the syringe.

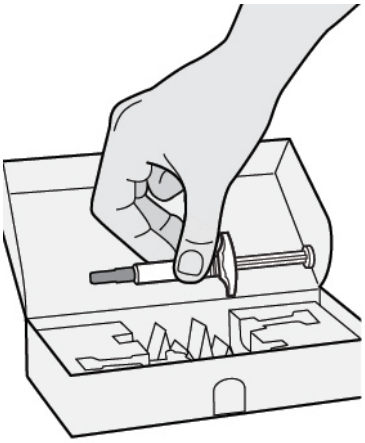
- **Do not** place the syringe into direct sunlight.

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*

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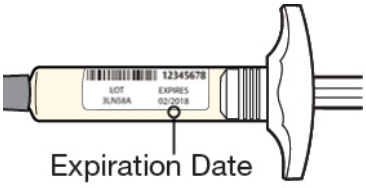


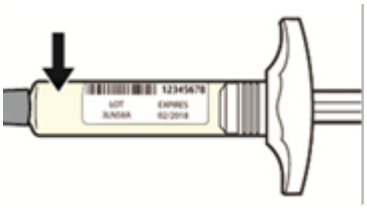
Step 3: Inspect

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.



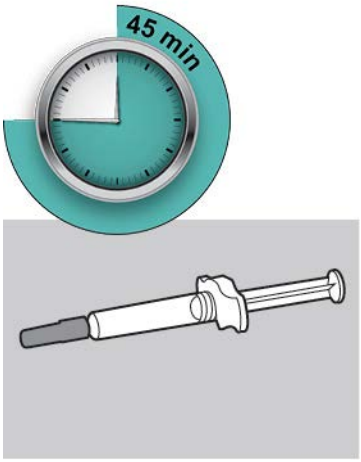
Step 4: Wait 45 minutes

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.

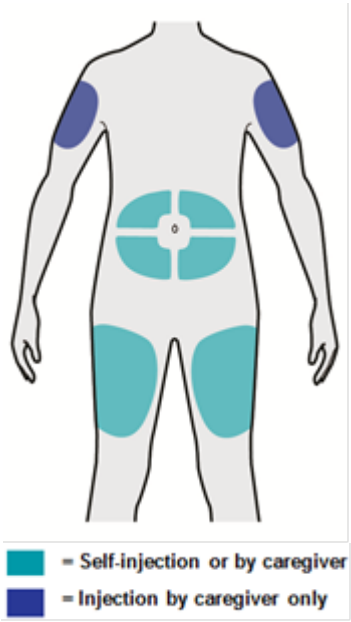


Step 5: Choose

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.

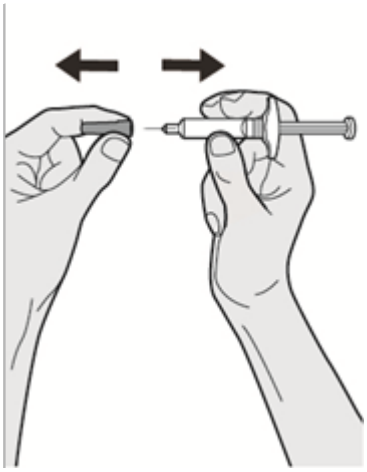
Step 7: Pull

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.

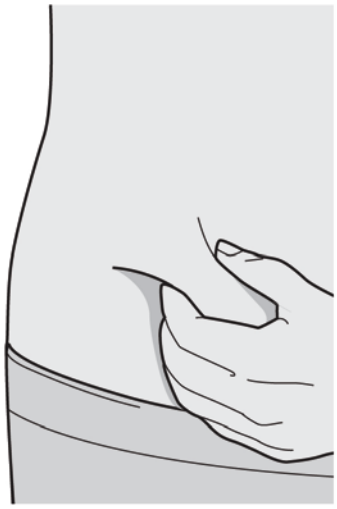
Do not touch the needle.

Inject your medicine immediately after removing the needle cap.



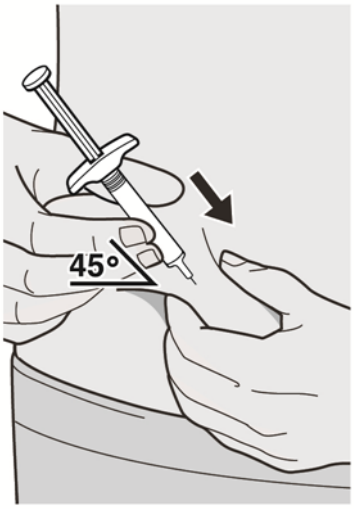
Step 8: Pinch

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 45º angle.

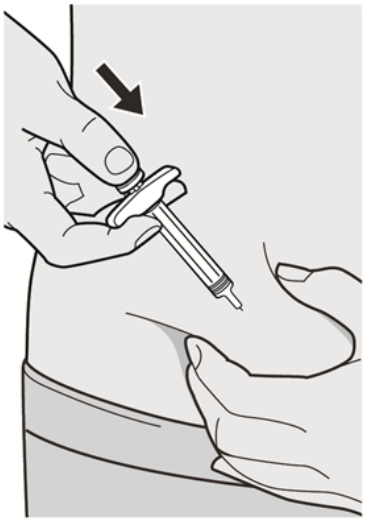


Step 10: Push

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.



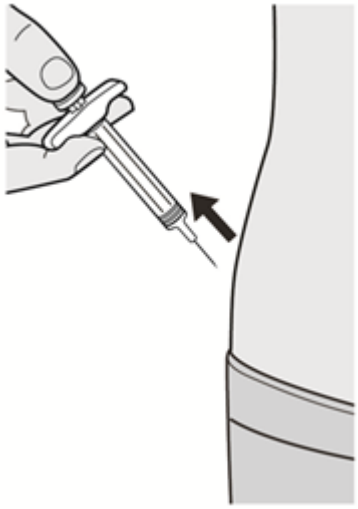
Step 11: Remove

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.**

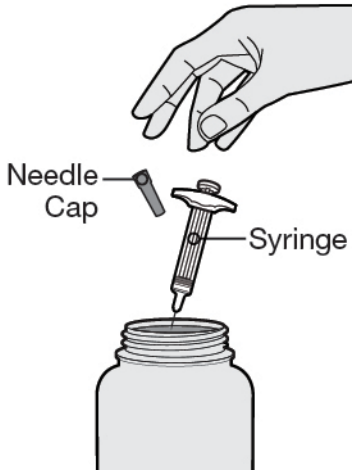


Step 12: Dispose

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.


Needle
Cap
Syringe

Package leaflet: Information for the user

Dupixent 200 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

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 asthma.

Dupixent is used to treat adults and adolescents 12 years and older 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.

Dupixent is used with other asthma medicines for the maintenance treatment of severe asthma in adults and adolescents (12 years of age and older) whose asthma is not controlled with their current asthma medicines. Dupixent helps prevent severe asthma attacks (exacerbations) and can improve your breathing. Dupixent may also help reduce the amount of another group of medicines you need to control your asthma, called oral corticosteroids, while preventing severe asthma attacks and improving your breathing.

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:

Dupixent is not a rescue medicine and should not be used to treat a sudden asthma attack.

Allergic reactions
Very rarely, Dupixent can cause serious side effects, including allergic (hypersensitivity) reactions and anaphylactic reaction. You must look out for signs of these conditions (i.e. breathing problems, swelling of the face, mouth, and tongue, fainting, dizziness, feeling lightheaded (low blood pressure), 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.

Eosinophilic conditions
Rarely patients taking an asthma medicine may develop inflammation of blood vessels or lungs due to an increase of certain white blood cells (eosinophilia). It is not known whether this is caused by Dupixent. This usually, but not always, happens in people who also take a steroid medicine which is being stopped or for which the dose is being lowered. Tell your doctor immediately if you develop a combination of symptoms such as a flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash.

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 or if your asthma remains uncontrolled or worsens during treatment with this medicine.

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

Children and adolescents

The safety and benefits of Dupixent are not yet known in children and adolescents with atopic dermatitis below the age of 12.

The safety and benefits of Dupixent are not yet known in children with asthma below the age of 12.

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.

Do not stop or reduce your asthma medicines, unless instructed by your doctor. These medicines (especially ones called *corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Dupixent.

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 200 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.

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).

Recommended dose in adolescents with atopic dermatitis
The recommended dose of Dupixent for adolescents (12 to 17 years of age) with atopic dermatitis is based on body weight:

Body Weight of Patient	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Recommended dose in adult and adolescent patients with asthma
For asthma, the recommended dose of Dupixent for adult and adolescents patients (12 years of age and older) is:

- An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

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 pre-filled syringe contains one dose of Dupixent (200 mg). Do not shake the pre-filled syringe.

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

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, including anaphylactic reaction; the signs of allergic reaction or anaphylactic reaction may include:
- breathing problems
- swelling of the face, mouth, and tongue
- fainting, dizziness, feeling lightheaded (low blood pressure)
- 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) atopic dermatitis and asthma:
- injection site reactions (i.e. redness, swelling, and itching)

Common (may affect up to 1 in 10 people) atopic dermatitis only:
- 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 200 mg of dupilumab in 1.14 ml solution for injection (injection).
- The other ingredients are arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 pre-filled syringe.

Dupixent is available as 200 mg pre-filled syringes 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.

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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

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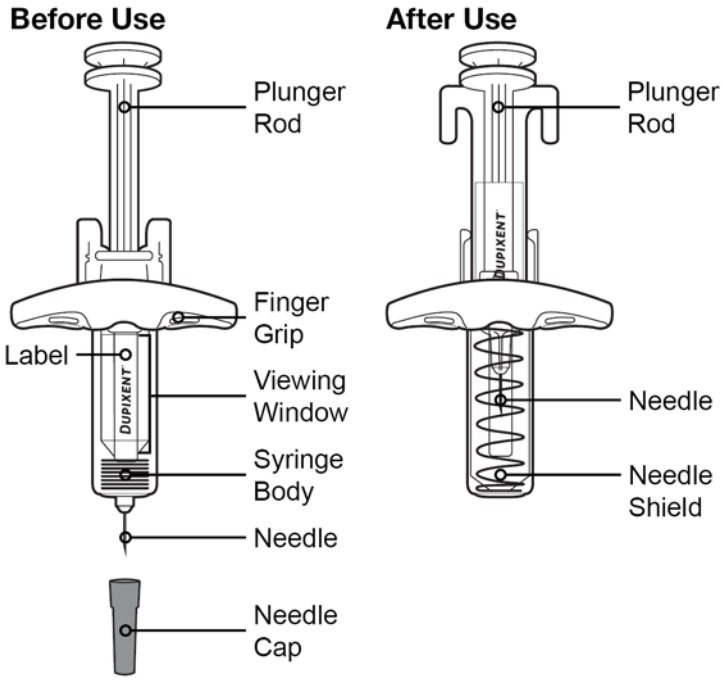
Dupixent 200 mg solution for injection in a pre-filled syringe with needle shield
dupilumab

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 200 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. In adolescents 12 years and older, it is recommended that Dupixent be administered by or under supervision of an adult.

- 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.

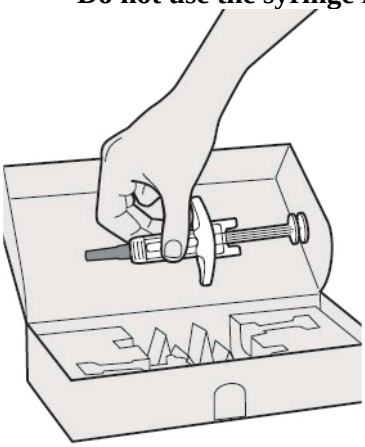
- Keep unused syringes in the original carton and store in the refrigerator between 2ºC and 8ºC.
- **Do not** keep Dupixent at room temperature (< 25ºC) for more than 14 days. If you need to permanently remove the carton from the refrigerator, write down the date of removal in the space provided on the 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 dropped on a hard surface or damaged.



Step 2: Prepare

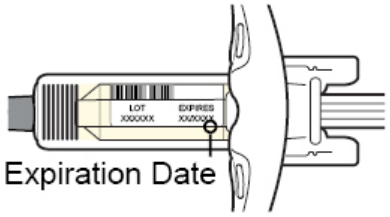
Ensure you have the following:
- the Dupixent pre-filled syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 12)

**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.



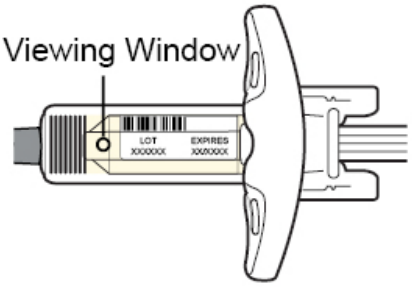
Step 3: Inspect

Look at the medicine 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.



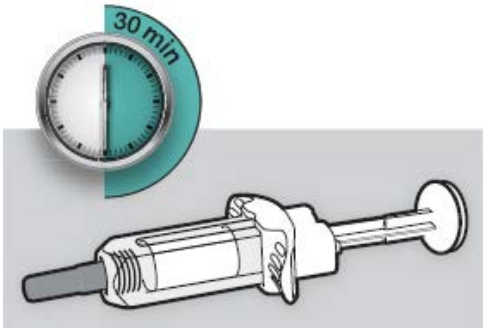
Step 4: Wait 30 minutes

Lay the syringe on a flat surface for at least 30 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.

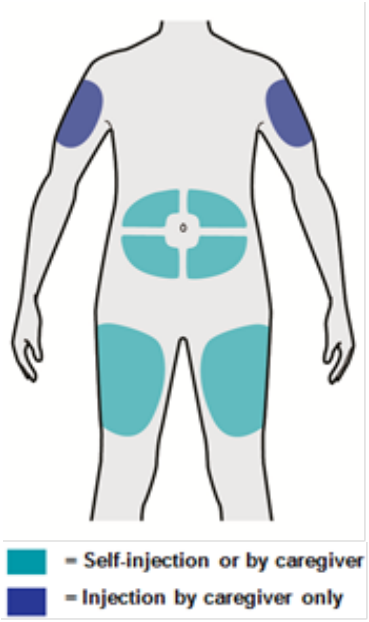


Step 5: Choose

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.

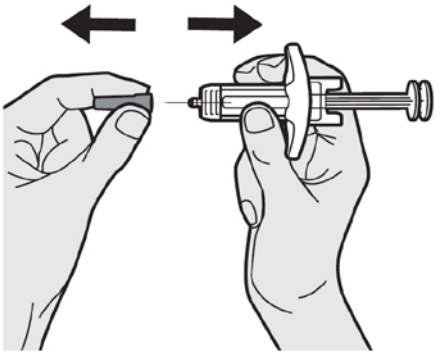
Step 7: Pull

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.

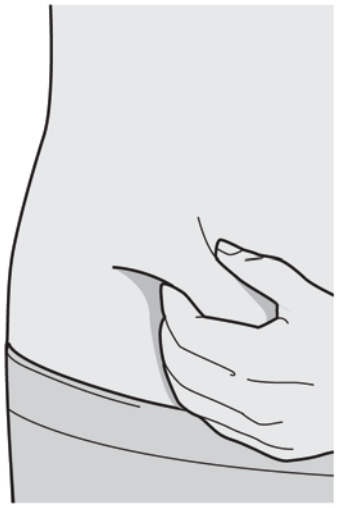
Do not touch the needle.

Inject your medicine immediately after removing the needle cap.



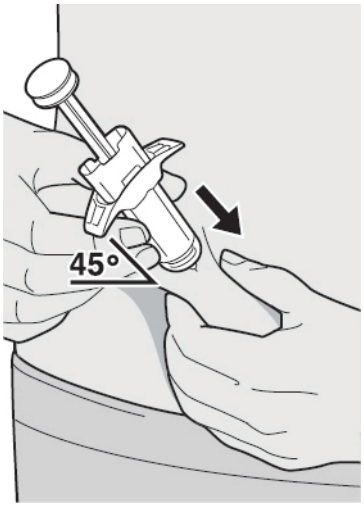
Step 8: Pinch

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



Step 9: Insert

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

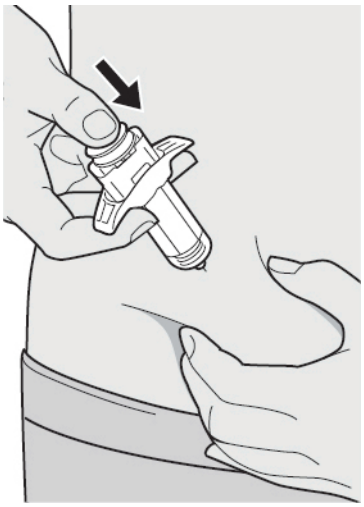


Step 10: Push

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.



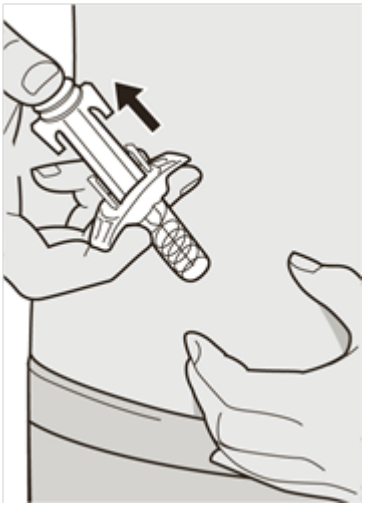
Step 11: Release and Remove

Lift your thumb to release the plunger rod until the needle is covered by the needle shield and then remove the syringe from the injection site.

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

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

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

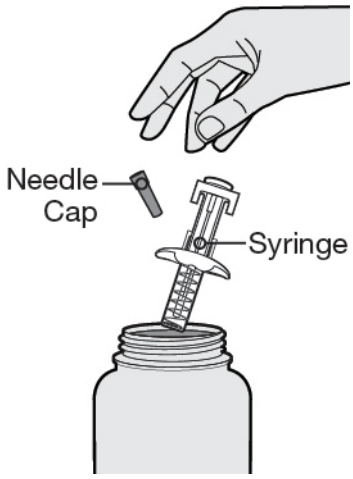


Step 12: Dispose

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.



Package leaflet: Information for the user

Dupixent 200 mg solution for injection in pre-filled pen
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

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 asthma.

Dupixent is used to treat adults and adolescents 12 years and older 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.

Dupixent is used with other asthma medicines for the maintenance treatment of severe asthma in adults and adolescents (12 years of age and older) whose asthma is not controlled with their current asthma medicines. Dupixent helps prevent severe asthma attacks (exacerbations) and can improve your breathing. Dupixent may also help reduce the amount of another group of medicines you need to control your asthma, called oral corticosteroids, while preventing severe asthma attacks and improving your breathing.

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:

Dupixent is not a rescue medicine and should not be used to treat a sudden asthma attack.

Allergic reactions
Very rarely, Dupixent can cause serious side effects, including allergic (hypersensitivity) reactions and anaphylactic reaction. You must look out for signs of these conditions (i.e. breathing problems, swelling of the face, mouth, and tongue, fainting, dizziness, feeling lightheaded (low blood pressure), 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.

Eosinophilic conditions
Rarely patients taking an asthma medicine may develop inflammation of blood vessels or lungs due to an increase of certain white blood cells (eosinophilia). It is not known whether this is caused by Dupixent. This usually, but not always, happens in people who also take a steroid medicine which is being stopped or for which the dose is being lowered. Tell your doctor immediately if you develop a combination of symptoms such as a flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash.

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 or if your asthma remains uncontrolled or worsens during treatment with this medicine.

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

Children and adolescents

The safety and benefits of Dupixent are not yet known in children and adolescents with atopic dermatitis below the age of 12.

The safety and benefits of Dupixent are not yet known in children with asthma below the age of 12.

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.

Do not stop or reduce your asthma medicines, unless instructed by your doctor. These medicines (especially ones called *corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Dupixent.

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 200 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.

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).

Recommended dose in adolescents with atopic dermatitis
The recommended dose of Dupixent for adolescents (12 to 17 years of age) with atopic dermatitis is based on body weight:

Body Weight of Patient	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Recommended dose in adult and adolescent patients with asthma
For asthma, the recommended dose of Dupixent for adult and adolescents patients (12 years of age and older) is:

- An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

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 pre-filled pen contains one dose of Dupixent (200 mg). Do not shake the pre-filled pen.

Read the “Instructions for Use” for the pre-filled pen carefully before using Dupixent.

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, including anaphylactic reaction; the signs of allergic reaction or anaphylactic reaction may include:
- breathing problems
- swelling of the face, mouth, and tongue
- fainting, dizziness, feeling lightheaded (low blood pressure)
- 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) atopic dermatitis and asthma:
- injection site reactions (i.e. redness, swelling, and itching)

Common (may affect up to 1 in 10 people) atopic dermatitis only:
- 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 pens 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 pen contains 200 mg of dupilumab in 1.14 ml solution for injection (injection).
- The other ingredients are arginine hydrochloride, histidine, polysorbate 80, sodium acetate, glacial 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 pre-filled pen.

Dupixent is available as 200 mg pre-filled pens in a pack containing 1, 2, 3, or 6 pre-filled pens.

Not all pack sizes may be marketed.

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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

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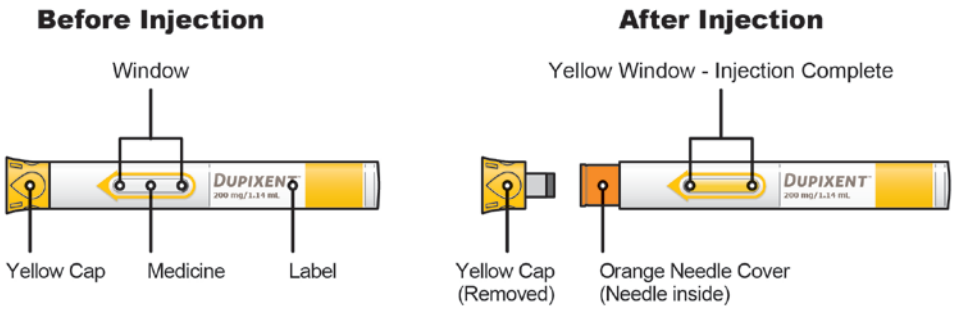
Dupixent 200 mg solution for injection in a pre-filled pen
Dupilumab

Instructions for use

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



Important information
This device is a single-use pre-filled pen. It contains 200 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. In adolescents 12 years and older, it is recommended that Dupixent be administered by or under supervision of an adult.

- Read all of the instructions carefully before using the pre-filled pen.
- Ask your healthcare professional how often you will need to inject the medicine.
- Choose a different injection site for each injection
- **Do not** use the pre-filled pen if it has been damaged.
- **Do not** use the pre-filled pen if the yellow cap is missing or not securely attached.
- **Do not** press or touch the orange needle cover with your fingers.
- **Do not** inject through clothes.
- **Do not** remove the yellow cap until just before you give the injection.
- **Do not** try to put the yellow cap back on the pre-filled pen.
- **Do not** re-use the pre-filled pen.

How to Store Dupixent

- Keep the pre-filled pen(s) and all medicines out of the reach of children.
- Keep unused pre-filled pens in the original carton and store in the refrigerator between 2ºC and 8ºC.
- Store pre-filled pens in the original carton to protect it from light.
- **Do not** keep pre-filled pens at room temperature (<25ºC) 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 pre-filled pen at any time.
- **Do not** heat the pre-filled pen.
- **Do not** freeze the pre-filled pen.
- **Do not** place the pre-filled pen into direct sunlight.

A: Prepare
A1. Gather supplies

Ensure you have the following:

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

**Items not included in the carton*

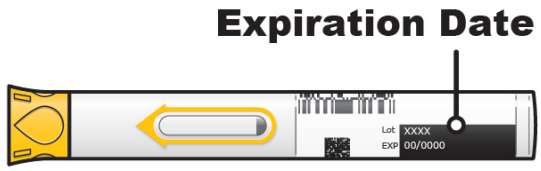
A2. Look at the label

- Confirm that you have the correct product and dose.

A. Check expiration date

- Check the expiration date.

⚠ **Do not use the pre-filled pen if the expiration date has passed.**



A4. Check the medicine

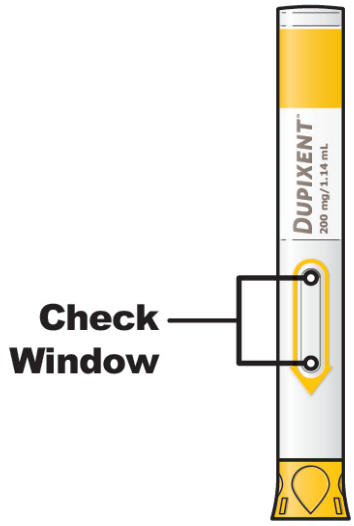
Look at the medicine through the window on the pre-filled pen.

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 pre-filled pen if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**

⚠ **Do not use the pre-filled pen if the window is yellow.**



A5: Wait 30 minutes

Lay the pre-filled pen on a flat surface and let it naturally warm up at room temperature (less than 25ºC) for at least 30 minutes.

⚠ **Do not heat the pre-filled pen.**

⚠ **Do not put the pre-filled pen into direct sunlight.**

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

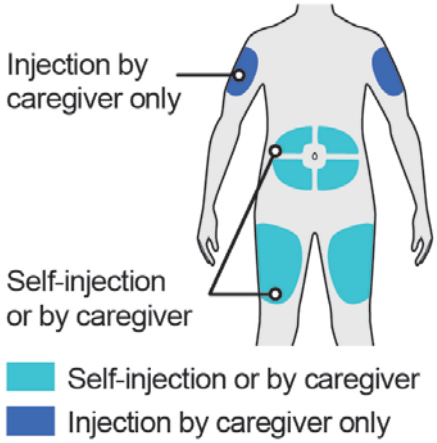
B. Choose your injection site
B1. Recommended injection sites are:

- **Thigh**
- **Stomach** except for the 5 cm around your belly button (navel).
- **Upper Arm** If a caregiver gives your dose, they can also use the outer area of the upper arm.

Choose a different injection site for each Dupixent injection.

⚠ **Do not inject through clothes.**

⚠ **Do not inject into skin that is tender, damaged, bruised or scarred.**

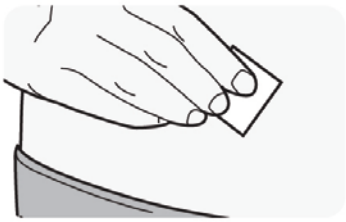


B2. Wash your hands

B3. Prepare the injection site

- 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.**



C. Give injection
C1. Remove yellow cap

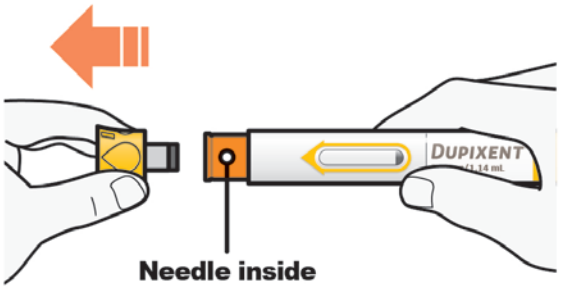
Pull the yellow cap straight off.

Do not twist the yellow cap off.

Do not remove the yellow cap until you are ready to inject.

Do not press or touch the orange needle cover with your fingers. The needle is inside.

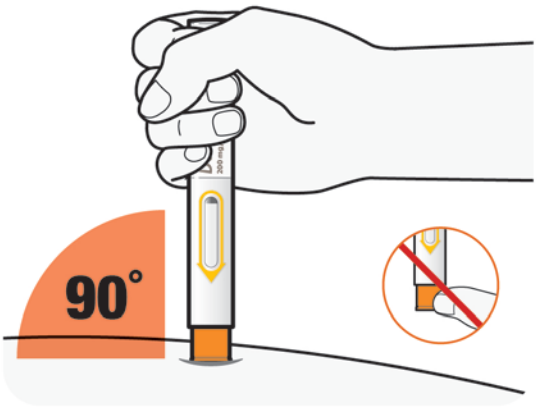
⚠ **Do not put the yellow cap back on the pre-filled pen after you have removed it.**



C2. Place

- When placing the orange needle cover on your skin, hold the pre-filled pen so that you can see the window.
- Place the orange needle cover on your skin at approximately a 90-degree angle.

⚠ **Do not press or touch the orange needle cover with your fingers. The needle is inside.**

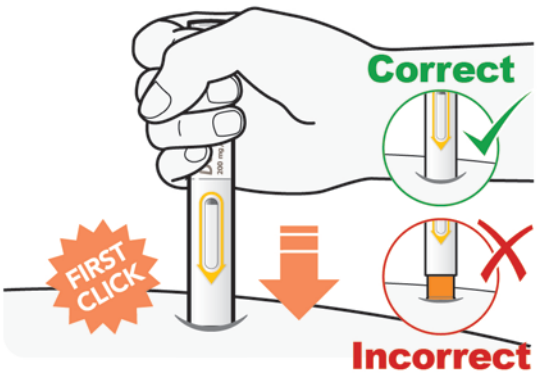


C3. Press down

Press the pre-filled pen firmly against your skin until you cannot see the orange needle cover, and hold.

- There will be a “click” when the injection starts.
- The window will start to turn yellow.

The injection can take up to 20 seconds.



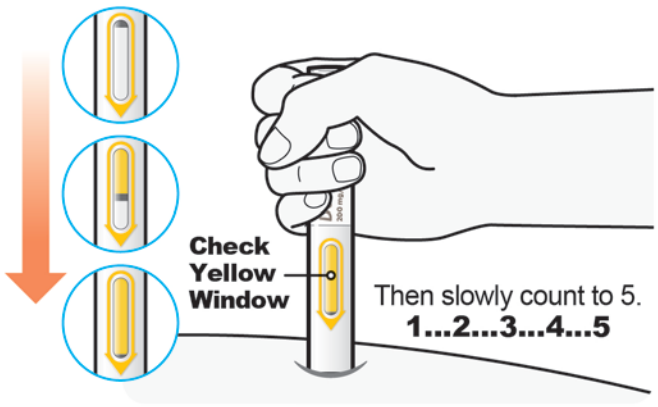
C4. Hold firmly

Keep holding the pre-filled pen firmly against your skin.

- You may hear a second click.
- Check that the entire window has turned to yellow.
- Then slowly count to 5.
- Then lift the pen up off the skin, your injection is complete.

If the window does not turn completely yellow, remove the pen and call your healthcare provider.

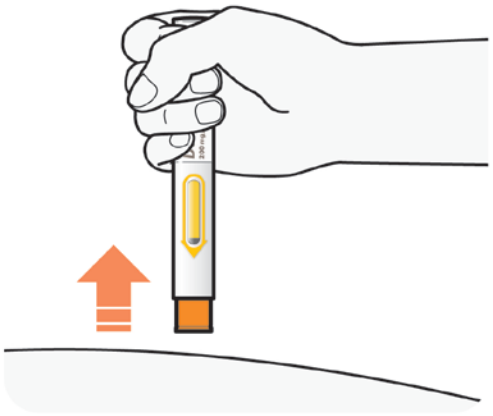
⚠ **Do not give yourself a second dose without speaking to your healthcare provider.**



C5. Remove

- After you have completed your injection pull straight up to remove pre-filled pen from the skin.
- If you see any blood at the site, lightly dab a cotton ball or gauze pad.

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



D. Dispose

- Dispose of the pre-filled pens, (needle inside), and yellow caps in a puncture resistant container right away after use.

Do not dispose of (throw away) pre-filled pens (needle inside), and yellow caps in your household trash.

⚠ **Do not put the yellow cap back on.**