| For the use only of a Registered Medical Practitioner or Hospital or a Laboratory |
|---|
| This package insert is continually updated. Please read carefully before using a new pack |
| WARNING: To be sold by retail on the prescription of Registered Dermatologist only |

# Dupilumab 150 mg/ml solution for Injection

**DUPIXENT®**

Pre-filled syringe with needle shield

## ACTIVE INGREDIENTS

Dupixent® is a fully human monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes. Dupixent® 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).

Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Dupilumab is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. There is a single N-linked glycosylation site in each heavy chain, located within the CH2 domain of the Fc constant region of the molecule. The Dupixent® heavy chain has an immunoglobulin (Ig) $G4^P$ isotope constant region. $IgG4^P$ is an IgG4 constant region with a single amino acid substitution in the hinge region that recreates the IgG1 hinge sequence in order to stabilize IgG4 dimer formation. The variable domains of the heavy and light chains combine to form the IL-4Rα binding site within the antibody. Dupilumab has a molecular weight of approximately 147 kDa.

## THERAPEUTIC OR PHARMACOLOGICAL CLASS

Immunomodulators, Interleukin inhibitors.
ATC Code : D11AH05

## PHARMACEUTICAL FORM(S)

Solution for subcutaneous injection in a single-use pre-filled syringe and a single-use pre-filled syringe with needle shield. Clear to slightly opalescent, colorless to pale yellow solution, which is free from visible particulates.

## COMPOSITION

Active ingredient: dupilumab

Each single-use pre-filled syringe with needle shield contains 300 mg dupilumab in 2 mL solution.

Excipients:
L-arginine monohydrochloride (10.5mg), L-histidine (5.4mg), L-Histidine monohydrochloride monohydrate (1mg), Polysorbate 80 (4mg), Sodium acetate trihydrate (2.6mg), Glacial acetic acid (0.3mg), Sucrose (100mg) and Water for injection q.s.

**NATURE AND CONTENTS OF CONTAINER**
300mg Pre-Filled Syringe with needle shield

Dupixent® is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. Dupixent® is provided as a single dose in a 2.25-mL siliconized clear Type-1 glass pre-filled syringe with a fixed 27-gauge ½ inch, thin wall stainless steel staked needle and passive needle shield. The needle cap is not made with natural rubber latex.

Each pre-filled syringe with needle shield is designed to deliver 300 mg of Dupixent® in 2 mL (150 mg/mL) solution.

**INDICATIONS**
Dupixent® is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

**DOSAGE AND ADMINISTRATION**
**GENERAL**
Dupixent® is administered by subcutaneous injection.

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

Based on individual therapeutic response, the dosage may be increased to 300 mg given weekly.

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

**SPECIAL POPULATIONS**

***Pediatric patients***
Safety and efficacy in pediatric patients with atopic dermatitis younger than 12 years have not been established.
***Elderly patients***
No dose adjustment is recommended for elderly patients.
***Hepatic impairment***
No data are available in patients with hepatic impairment.
***Renal impairment***
No dosage adjustment is needed in patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment.
***Body weight***
No dose adjustment for body weight is recommended.

**ADMINISTRATION**
For the initial 600 mg dose, administer two 300 mg Dupixent® injections consecutively in different injection sites.

Dupixent® is intended for use under the guidance of a healthcare provider. A patient may self-inject Dupixent® or the patient's caregiver may administer Dupixent®.

Dupixent® is self-administered by **subcutaneous injection** into the thigh or abdomen, except for the 2 inches (5 cm) around the navel, using a single-use pre-filled syringe. If somebody else administers the injection, the upper arm can also be used.

It is recommended to **rotate the injection site with each injection**.

**Dupixent® should not be injected into skin that is tender, damaged or has bruises or scars.**

## CONTRAINDICATIONS

Dupixent® is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients.

## WARNINGS AND PRECAUTIONS FOR USE

### Hypersensitivity

If a systemic hypersensitivity reaction occurs, administration of Dupixent® should be discontinued immediately and appropriate therapy initiated. One case of serum sickness-like reaction and one case of serum sickness reaction, both considered serious, have been reported in clinical trials following the administration of Dupixent®.

### Conjunctivitis

Conjunctivitis occurred more frequently in atopic dermatitis patients who received Dupixent®. Most patients with conjunctivitis recovered or were recovering during the treatment period. Patients should report new onset or worsening eye symptoms to their healthcare provider.

### Helminth Infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if Dupixent® will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating Dupixent®. If patients become infected while receiving treatment with Dupixent® and do not respond to anti-helminth treatment, discontinue treatment with Dupixent® until infection resolves.

### Concomitant Atopic Conditions

Patients with atopic dermatitis who have comorbid asthma should be advised not to adjust their treatment without consultation with their physicians. When discontinuing Dupixent® consider the potential effects on other atopic conditions.

## INTERACTIONS

### Live Vaccines:

Dupixent® has not been studied with live vaccines.
Live vaccines should not be given concurrently with Dupixent®

### Non-Live Vaccines:

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, Adacel®) and a meningococcal polysaccharide vaccine (T cell-independent, Menomune®) 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.

### Interactions with CYP450 Substrates:

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

**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. Dupixent® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**LACTATION**
It is unknown whether dupilumab is excreted in human milk. Because many drugs could be excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue Dupixent® therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
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**DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS**
Dupixent® has no or negligible influence on the ability to drive or operate machinery.

**ADVERSE REACTIONS**
In the overall exposure pool, a total of 2526 patients with atopic dermatitis were treated with Dupixent® in controlled and uncontrolled clinical trials. Of these, 739 patients were exposed for at least 1 year.

The safety of Dupixent® monotherapy was evaluated through week 16 based on data from three randomized, double-blind, placebo-controlled multicenter studies (SOLO 1, SOLO 2, and a phase 2, dose-ranging study) that included 1564 adult patients with moderate-to-severe atopic dermatitis (AD). The study population had a mean age of 38.2 years, 41.1 % was female, 67.9 % white, 21.9 % Asian, 7.1% black, and reported co-morbid atopic conditions such as asthma (39.6%), allergic rhinitis (49.0%), food allergy (37.3%), and allergic conjunctivitis (23.1%).

The safety of Dupixent® with concomitant topical corticosteroids (TCS) was evaluated based on data from one randomized, double-blind, placebo-controlled multicenter study (CHRONOS). A total of 740 patients were treated up to 52 weeks. The study population had a mean age of 37.1 years, 39.7% was female, 66.2% white, 27.2% Asian, 4.6% black, and reported co-morbid atopic conditions such as asthma (39.3%), allergic rhinitis (42.8%), food allergy (33.4%), and allergic conjunctivitis (23.2%).

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9% of the placebo group, 1.9% of the Dupixent® 300 mg Q2W group, 1.5% of the Dupixent® 300 mg QW group. One patient on Dupixent® discontinued treatment due to an adverse reaction: conjunctivitis allergic.

In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6% of the placebo + TCS group, 1.8% of the Dupixent® 300 mg Q2W + TCS group, and 2.9% of the Dupixent® 300 mg QW + TCS group. Three patients on Dupixent® discontinued treatment due to an adverse reaction: injection site reaction (2 patients) and eye pruritus (1 patient).

Table 1 summarizes the adverse reactions that occurred in ≥1% of patients treated with Dupixent® during the first 16-weeks of treatment in placebo-controlled trials.

**Table 1: Adverse Reactions Occurring in ≥1% of Patients with Atopic Dermatitis Treated with Dupixent® Through Week 16 in Placebo-controlled Trials**.

| Adverse Reaction | Dupixent®) Monotherapy [a] | | | Dupixent®+ TCS [b] | | |
|---|---|---|---|---|---|---|
| | Placebo N=517 n (%) | Dupixent® 300 mg Q2W N=529 n (%) | Dupixent® 300 mg QW N=518 n (%) | Placebo +TCS N=315 n (%) | Dupixent ® 300 mg Q2W + TCS N=110 n (%) | Dupixent® 300 mg QW + TCS N=315 n (%) |
| **Injection site reactions** | 28 (5.4%) | 51 (9.6%) | 72 (13.9%) | 18 (5.7%) | 11 (10.0%) | 50 (15.9%) |
| **Conjunctivitis allergic** | 5 (1.0%) | 16 (3.0%) | 12 (2.3%) | 10 (3.2%) | 7 (6.4%) | 22 (7.0%) |
| **Blepharitis** | 1 (0.2%) | 2 (0.4%) | 6 (1.2%) | 2 (0.6%) | 5 (4.5%) | 8 (2.5%) |
| **Conjunctivitis** | 3 (0.6%) | 21 (4.0%) | 20 (3.9%) | 1 (0.3%) | 0 | 1 (0.3%) |
| **Oral herpes** | 8 (1.5%) | 20 (3.8%) | 13 (2.5%) | 5 (1.6%) | 3 (2.7%) | 8 (2.5%) |
| **Eye pruritus** | 1 (0.2%) | 3 (0.6%) | 2 (0.4%) | 2 (0.6%) | 2 (1.8%) | 9 (2.9%) |
| **Conjunctivitis bacterial** | 2 (0.4%) | 7 (1.3%) | 8 (1.5%) | 2 (0.6%) | 1 (0.9%) | 6 (1.9%) |
| **Dry eye** | 0 | 1 (0.2%) | 6 (1.2%) | 1 (0.3%) | 2 (1.8%) | 3 (1.0%) |
| **Herpes simplex** [c] | 4 (0.8%) | 9 (1.7%) | 4 (0.8%) | 1 (0.3%) | 1 (0.9%) | 4 (1.3%) |
| **Eosinophilia** | 2 (0.4%) | 9 (1.7%) | 1 (0.2%) | 0 | 1 (0.9%) | 1 (0.3%) |

a Safety data from a phase 2, dose-ranging study and the SOLO 1and SOLO 2 studies.
b Safety data from the CHRONOS study. Patients were on background TCS therapy.
c In clinical trials, herpes simplex cases were mucocutaneous, generally mild to moderate in severity, and did not include eczema herpeticum. Eczema herpeticum cases were reported separately and incidence was lower in patients treated with Dupixent® compared to placebo.

The safety profile of Dupixent®+ TCS through week 52 is consistent with the safety profile observed at week 16.

**DESCRIPTION OF SELECTED ADVERSE REACTIONS**

*Hypersensitivity*

In the overall exposure pool, there was one case reported as serum sickness reaction and one case reported as serum sickness-like reaction following administration of Dupixent®.

*Laboratory Abnormalities*

In clinical studies, transient elevations in blood eosinophils were observed after initiating Dupixent® treatment in a minority of patients. Eosinophilia was reported in <2% of patients treated with Dupixent® (see Table 1).

There were no other clinically significant laboratory abnormalities.

Overall Infections

No increase was observed in the overall incidence of infections or serious infections with Dupixent® compared to placebo in clinical studies. In the 16-week monotherapy clinical studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5% of patients treated with Dupixent®. In the 52-week CHRONOS study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2% of patients treated with Dupixent®.

Immunogenicity

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

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

ADA responses were not generally associated with impact on Dupixent® exposure, safety, or efficacy. In the overall exposure pool, less than 0.1% of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (<0.1%) associated with high ADA titers.

The observed incidence of persistent ADA responses and neutralizing activity in the assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease status of the individual patient. For these reasons, comparison of the incidence of antibodies to Dupixent with the incidence of antibodies to other products may be misleading.

**OVERDOSE**

SIGNS AND SYMPTOMS

In clinical studies, no safety issues were identified with single intravenous doses up to 12 mg/kg.

MANAGEMENT

There is no specific treatment for Dupixent® overdose.

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

**INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST**

Not applicable.

**ABUSE AND DEPENDENCE**

Not applicable.

**PHARMACODYNAMICS**

Mechanism of action

Dupixent® is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupixent® 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 key type 2 (including Th2) cytokines involved in atopic disease.

**Pharmacodynamic Properties**

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

Dupixent® suppressed TARC relative to placebo as early as week 2, with a trend of continued decline to a

maximal and sustained suppression by Week 12. The majority of patients treated with Dupixent® in the CHRONOS study (87.0% and 84.9% of patients in the Dupixent® 300 mg Q2W and 300 mg QW, respectively) achieved normalized TARC levels compared to 20.0% in the placebo group at week 52.

Total IgE was reduced -74.8% and -73.9% by Week 52 (median change from baseline) with Dupixent® 300 mg Q2W and 300 mg QW, respectively compared to -0% in the placebo group. Similar trends were observed for allergen specific IgEs. After 52 weeks of treatment, total IgE was normalized in 11.7% and 15.9% of patients receiving Dupixent® 300 mg Q2W and 300 mg QW, respectively compared to 4.4% in the placebo group. Similar trends were observed with antigen-specific IgEs, including S. aureus specific enterotoxin A, grass and tree allergens.

**CLINICAL EFFICACY/CLINICAL STUDIES**

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

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

- SOLO 1 enrolled 671 patients (224 to placebo, 224 to Dupixent® 300 mg Q2W, and 223 to Dupixent® 300 mg QW) and had a treatment period of 16 weeks.
- SOLO 2 enrolled 708 patients (236 to placebo, 233 to Dupixent® 300 mg Q2W, and 239 to Dupixent® 300 mg QW) and had a treatment period of 16 weeks.
- CHRONOS enrolled 740 patients (315 to placebo + TCS, 106 to Dupixent® 300 mg Q2W + TCS, and 319 to Dupixent® 300 mg QW + TCS) and had a treatment period of 52 weeks. Patients received Dupixent® or placebo with concomitant use of TCS starting at baseline using a standardized regimen. Patients were also permitted to use topical calcineurin inhibitors (TCI).

**Endpoints**

In all three pivotal studies, the 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% or 90% in EASI (EASI-50 or 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.

IGA reflects physician's overall assessment (whole body average) of AD skin lesions. EASI is a composite score (ranging from 0-72) based on the extent and severity of the AD lesions assessed systematically for erythema, induration/papulation/edema, excoriation, and lichenification for each anatomical region. The pruritus NRS is a patient-reported measure which assesses maximum itch intensity in the previous 24-hours using a 0-10-point scale (0 = no itch; 10 = worst itch imaginable). The SCORAD is used to assess extent and severity of AD signs and includes two visual analogue scales for symptoms (itch and sleep). The POEM

evaluates frequency of AD symptoms (including itch) and the impact of AD on sleep (score ranging from 0-28). The DLQI evaluates the health-related quality of life in dermatological patients (score ranging from 0-30). The HADS measures anxiety and depression symptoms (total score ranging from 0-42).

**Baseline Characteristics**
In the monotherapy studies (SOLO 1 and SOLO 2), across all treatment groups, 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, 53.1% of patients had a baseline IGA score of 3 and 46.9% of patients had a baseline IGA of 4 and 33.6 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 32.5, the baseline weekly pruritus NRS was 7.3, the baseline mean SCORAD score was 66.4, the baseline mean POEM score was 20.1, the baseline mean DLQI was 14.5, and the baseline mean HADS total score was 12.7.

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

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

Figure 1 and Figure 3 show the proportion of patients who achieved an IGA 0 or 1 response and EASI-75, respectively, up to Week 16.

Figure 2 shows the proportion of patients who achieved a > 4-point improvement on the pruritus NRS up to Week 16.

EASI-90 response at Week 16 was achieved in 7.6% of patients in the placebo group, 35.7% in the Dupixent® 300 mg Q2W group, and 33.2% in the Dupixent® 300 mg QW group, respectively in the SOLO 1 study and 7.2%, 30%, and 30.5% of patients, respectively in the SOLO 2 study.
EASI-50 response at Week 16 was achieved 24.6% of patients in the placebo group, 68.8% in the Dupixent® 300 mg Q2W group, and 61.0% in the Dupixent® 300 mg QW group, respectively in the SOLO 1 study and 22%, 65.2%, and 61.1% of patients, respectively in the SOLO 2 study.

**Table 2: Efficacy Results of Dupixent® Monotherapy at Week 16 (FAS)**

| | SOLO 1 (FAS)[a] | | | SOLO 2 (FAS)[a] | | |
|---|---|---|---|---|---|---|
| | **Placebo** | **'TM' 300 mg Q2W** | **'TM' 300 mg QW** | **Placebo** | **'TM' 300 mg Q2W** | **'TM' 300 mg QW** |
| ***Patients randomized*** | 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 | 12.3 % | 40.8 %[e] | 40.3 %[e] | 9.5% | 36.0 %[e] | 39.0 %[e] |

LS = least squares; SE= standard error

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

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

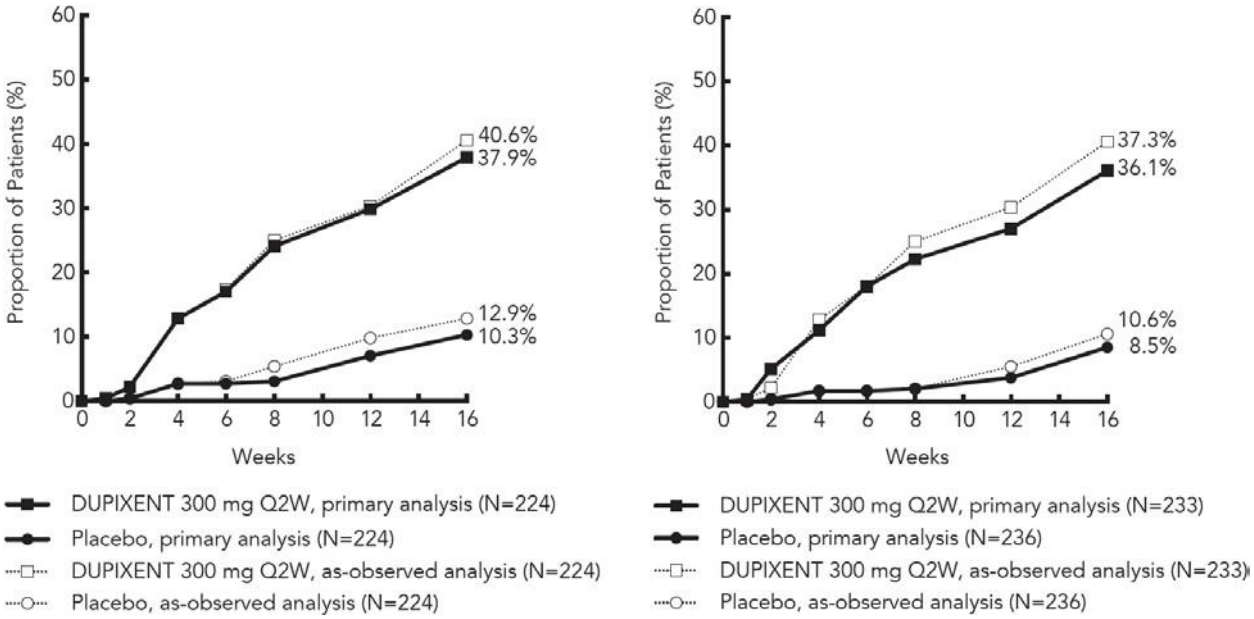
[c] Patients who received rescue treatment or with missing data were considered as non-responders.

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

[e] p-value <0.0001

**Figure 1: Proportion of patients with IGA 0 or 1[a] in SOLO 1[b] and SOLO 2 [b] (FAS)**

**SOLO 1** **SOLO 2**

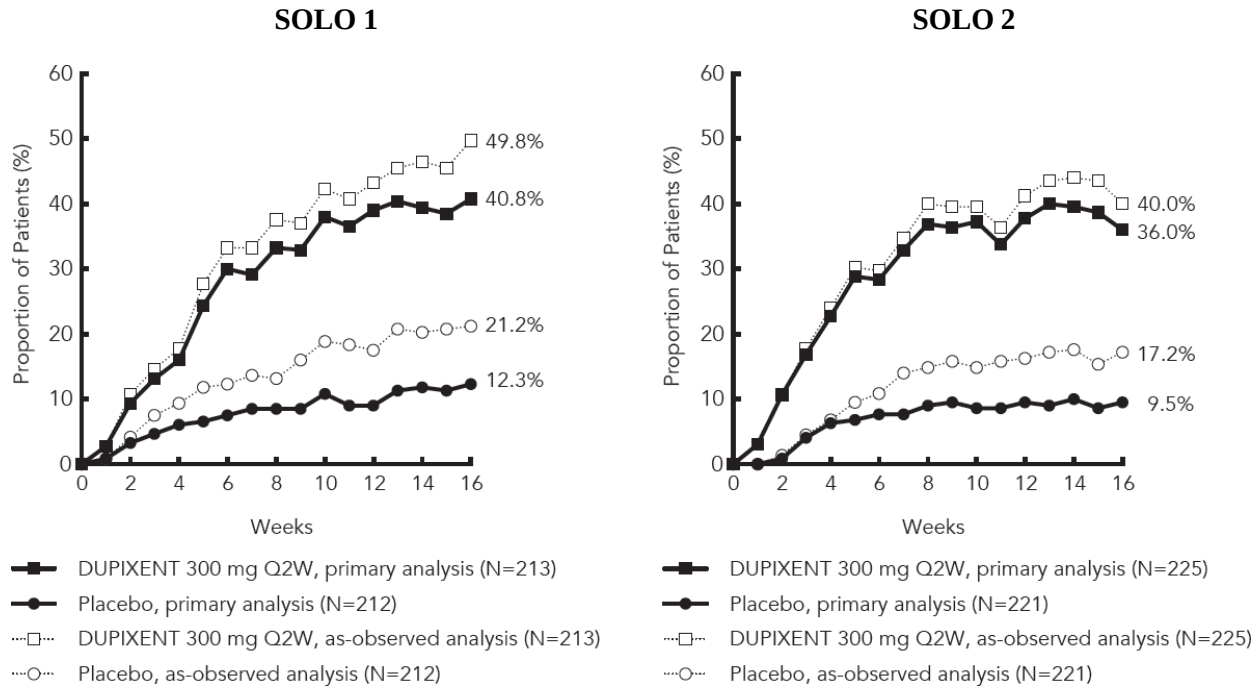



[a]Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.

[b]In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.

[c]Full analysis set (FAS) includes all patients randomized.

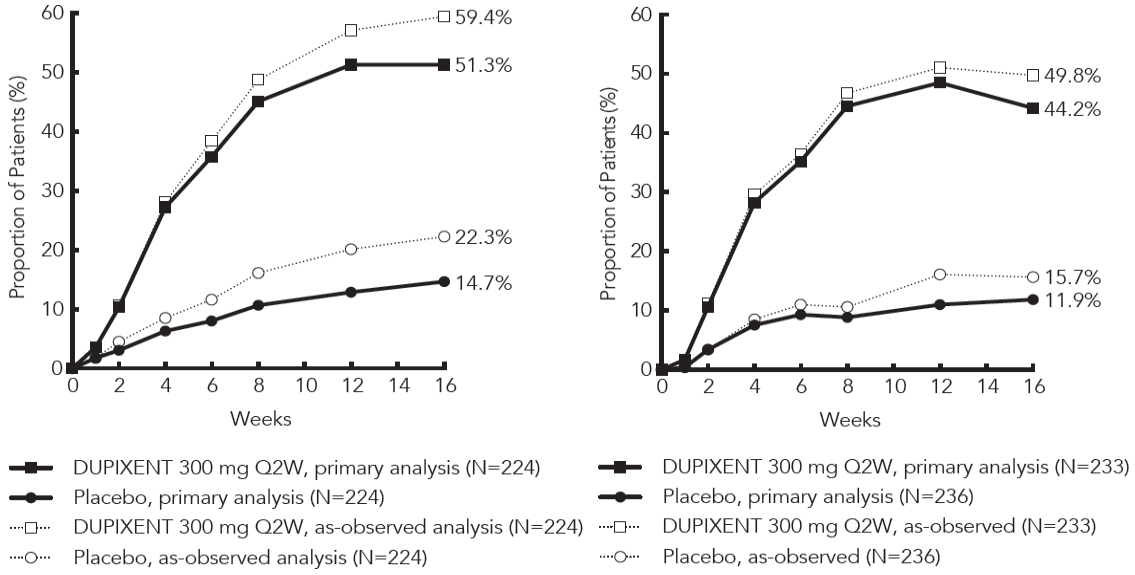
**Figure 2: Proportion of patients with ≥ 4-point improvement on the Pruritus NRS in SOLO 1 and SOLO 2 (FAS)**




[a]In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.
[b]Full analysis set (FAS) includes all patients randomized.

**Figure 3: Proportion of patients with EASI-75 in SOLO 1 and SOLO 2 (FAS)**

**SOLO 1** **SOLO 2**




[a]In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as 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 in general consistent with the results in the overall study population.

**52-Week Concomitant TCS Study (CHRONOS)**

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

A significantly greater proportion of patients randomized to Dupixent® + TCS achieved a rapid improvement in the pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement as early as week 2; $p<0.05$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period (see Figure 5). The improvement in pruritus NRS occurred in conjunction with the improvement of objective signs of atopic dermatitis.
Figure 4 and Figure 6 show the proportion of patients who achieved an IGA 0 or 1 response and EASI-75, respectively, up to Week 52 in CHRONOS.

Figure 5 shows the proportion of patients who achieved a ≥4-point improvement on the pruritus NRS up to Week 52.

EASI-90 response was achieved in 15.5% of patients in the placebo group, 50.6% in the Dupixent® 300 mg Q2W group, and 50.7% in the Dupixent® 300 mg QW group, respectively in the CHRONOS study at Week 52.

EASI-50 response was achieved 29.9% of patients in the placebo group, 78.7% in the Dupixent® 300 mg Q2W group, and 70.0% in the Dupixent® 300 mg QW group, respectively in the CHRONOS Study at Week 52.

**Table 3: Efficacy Results of Dupixent®) with Concomitant TCS[a] at Week 16 and Week 52 in CHRONOS**

| | **Week 16 (FAS)[b]** | | | **Week 52 (FAS Week 52)[b]** | | |
|---|---|---|---|---|---|---|
| | **Placebo + TCS** | **'TM' 300 mg Q2W + TCS** | **'TM' 300 mg QW + TCS** | **Placebo + TCS** | **'TM' 300 mg Q2W + TCS** | **'TM' 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 % (3.26) |
| ***Number of patients with baseline pruritus NRS score ≥4*** | 299 | 102 | 295 | 249 | 86 | 249 |

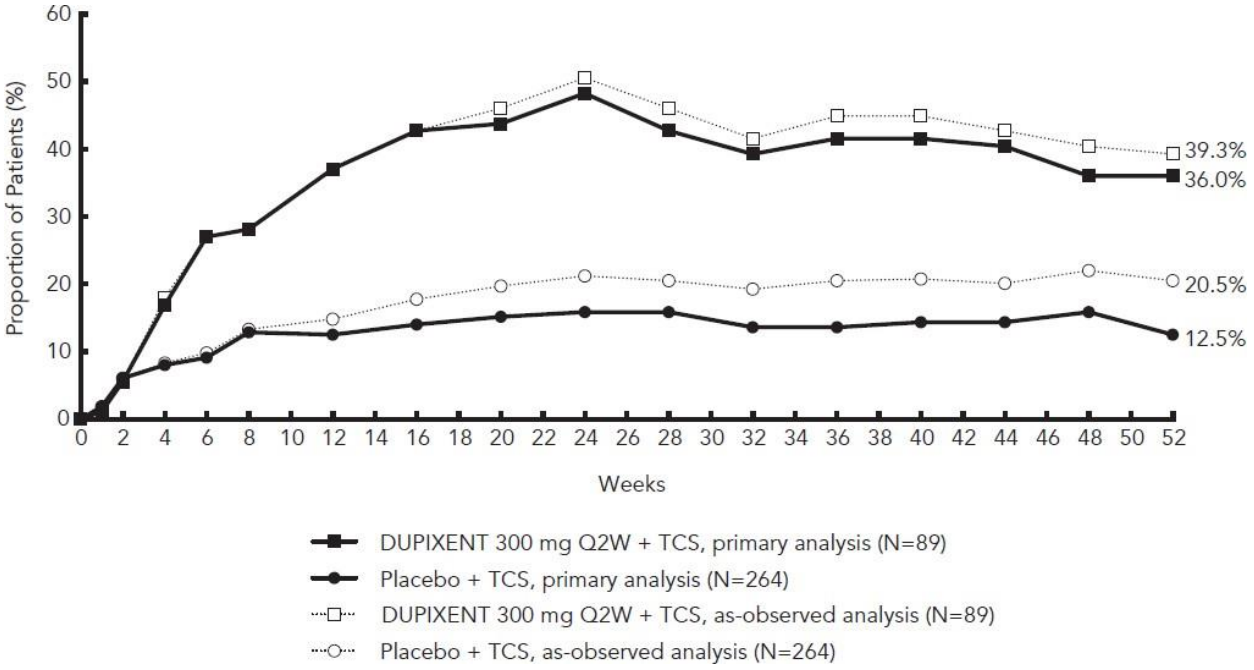
| | | | | | | |
|---|---|---|---|---|---|---|
| Pruritus NRS (≥4-point improvement), % responders[d, e] | 19.7 % | 58.8 %[f] | 50.8 %[f] | 12.9 % | 51.2 %[f] | 39.0 %[f] |

LS = least squares; SE = standard error

[a] All patients were on background TCS therapy and patients were permitted to use topical calcineurin inhibitors.
[b] Full analysis set (FAS) includes all patients randomized. FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.
[c] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on [a] 0-4 IGA scale.
[d] Patients who received rescue treatment or with missing data were considered as non-responders.
[e] a significantly greater proportion of patients on Dupixent had improvement in pruritus NRS of ≥4 points compared to placebo at week 2 ($p<0.05$).
[f] p-value <0.0001
[g] p-value = 0.0015
[h] p-value = 0.0003
[i] p-value = 0.0005

**Figure 4: Proportion of patients with IGA 0 OR 1 in CHRONOS (FAS 52 WEEK)[c]**

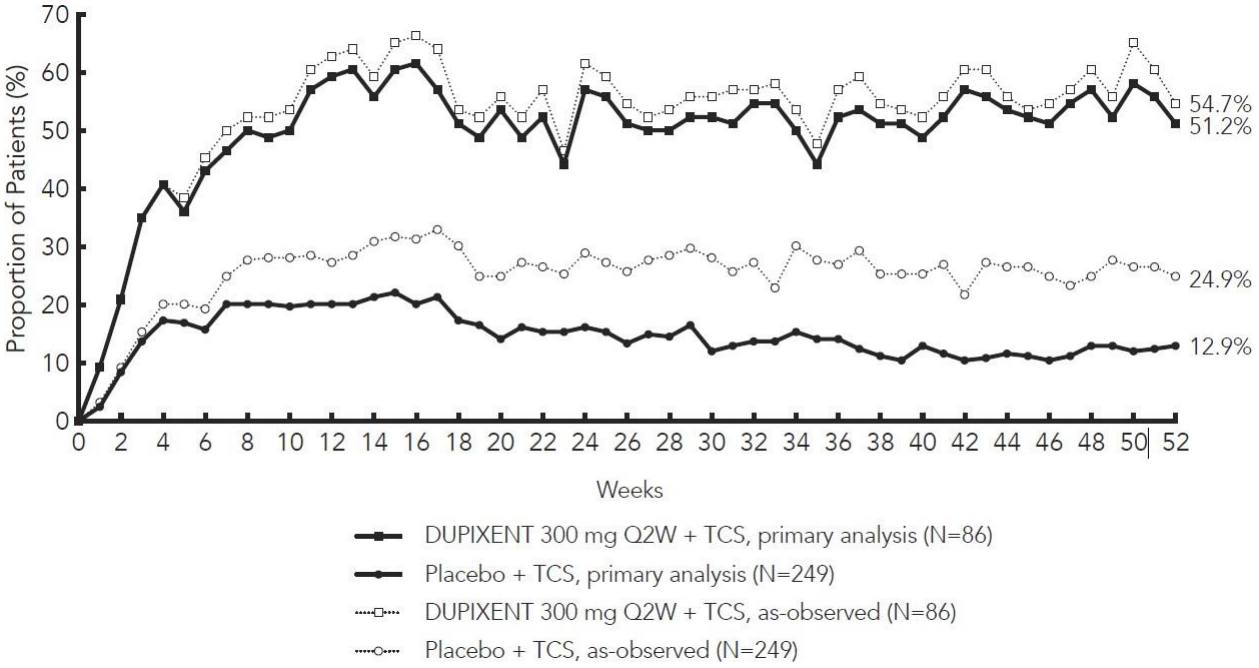
**CHRONOS**




[a] 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.
[b] In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.
[c] FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis

**Figure 5 : Proportion of Patients with ≥4 point improvement on the Pruritus NRS in CHRONOS[a] (FAS Week 52)[b]**

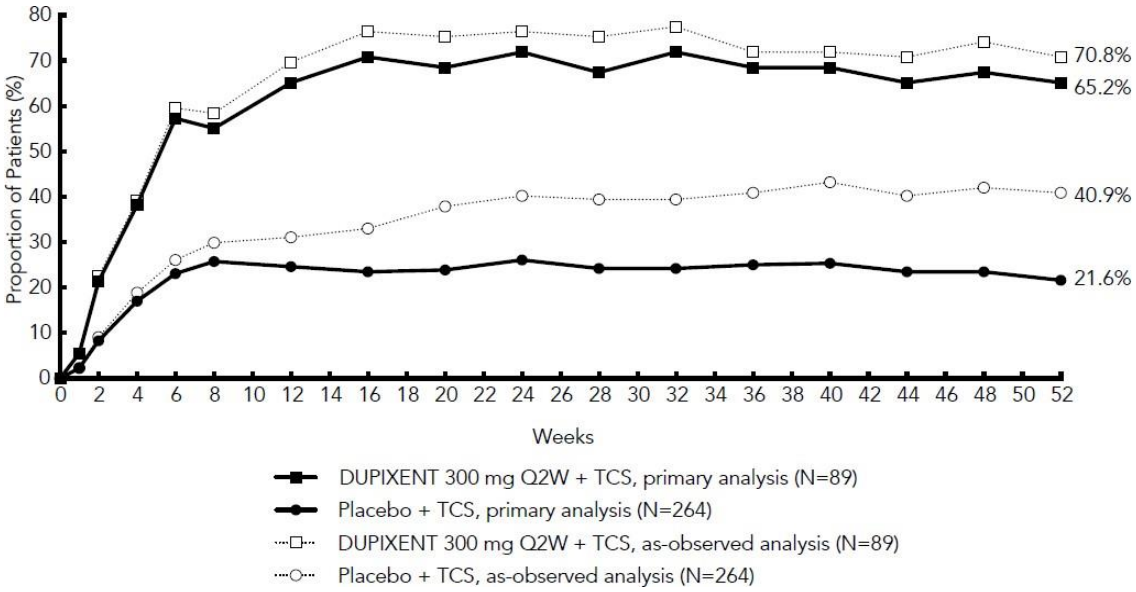
**CHRONOS**




[a]In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.

[b]FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

**Figure 6: Proportion of Patients with EASI-75 in CHRONOS [a] (FAS Week 52) [b]**
**CHRONOS**

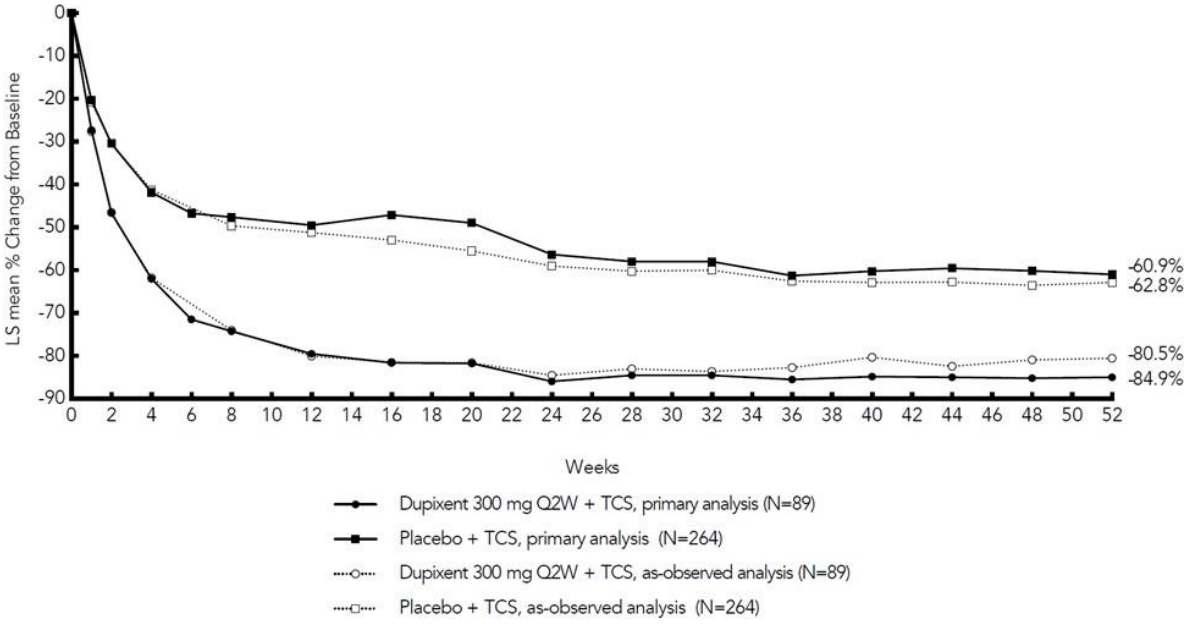



[a]In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as 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 evaluable subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in CHRONOS were in general consistent with the results in the overall study population.

Figure 7 and Figure 8 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.

**Figure 7: Mean Percent Change from baseline in EASI in CHRONOS[a] (FAS Week 52)[b]**

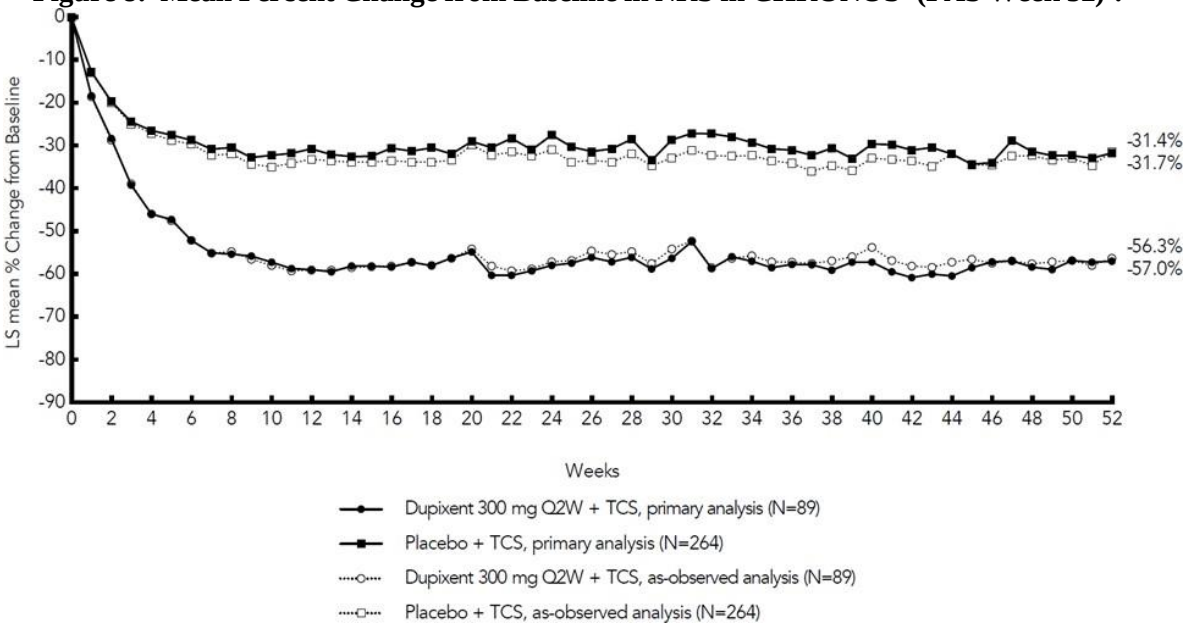



LS = least squares

[a] In the primary analyses of the efficacy endpoints (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.

[b] FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

**Figure 8: 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 (solid line above), patients who received rescue treatment were considered non-responders for the purpose of this statistical analysis. The as-observed analyses (dotted line above) included all data regardless of rescue treatment. In both cases, patients with missing data were considered as non-responders.
[b]FAS Week 52 includes all patients randomized at least one year before the cutoff date of the primary analysis.

**Clinical Response in Patients for whom Ciclosporin Treatment was Inadvisable**

In the monotherapy studies, across both Dupixent® treatment groups, patients for whom ciclosporin treatment was inadvisable (uncontrolled with or ineligible to receive ciclosporin), had generally more severe AD at baseline based on mean EASI (36.3 vs 31.4), IGA (3.6 vs 3.4), mean BSA involvement (58.9 % vs 52.5 %), peak pruritus NRS (7.5 vs 7.3) and DLQI (16.2 vs 14.5) scores relative to the remainder of patients in these studies. Similar findings were observed for patients for whom ciclosporin treatment was inadvisable in concomitant TCS study.

In patients for whom ciclosporin treatment was inadvisable, treatment with Dupixent® monotherapy, across both Dupixent® treatment groups, resulted in significant improvements in signs and symptoms of AD, compared to placebo-treated patients. A greater percentage of Dupixent®-treated patients than placebo-treated patients achieved IGA 0 or 1 and a reduction from baseline of ≥2 points at week 16 (29.5% vs 6.8%), EASI-75 at week 16 (38% vs 11.4%), and a ≥4 points reduction in pruritus NRS from baseline to week 16 (34.9% vs 8%) (p <0.001 for all 3 endpoints). Similar results were observed in patients who received Dupixent® concomitantly with TCS. The efficacy of Dupixent® + TCS was sustained at week 52.

**Additional Secondary Endpoints**

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

**Table 4 - Additional Secondary Endpoint Results of Dupixent® Monotherapy at Week 16**

| | **Monotherapy** | | | | | |
|---|---|---|---|---|---|---|
| | **SOLO 1 at Week 16** | | | **SOLO 2 at Week 16** | | |
| | **Placebo** | **'TM' 300 mg Q2W** | **'TM' 300 mg QW** | **Placebo** | **'TM' 300 mg Q2W** | **'TM' 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), Dupixent® 300 mg Q2W + TCS and 300 mg QW + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM and DLQI total scores, respectively, at 52 weeks compared to placebo + TCS. A larger proportion of patients administered Dupixent® 300 mg Q2W + TCS and 300 mg QW + TCS had clinically meaningful reductions in POEM and DLQI total score (each defined as ≥4-point improvement) from baseline to week 52 compared to the placebo + TCS. In addition, Dupixent® 300 mg Q2W + TCS and 300 mg QW + TCS reduced anxiety and depression as measured by the HADS total score at 52 weeks compared to placebo + TCS. In a post-hoc analysis in a subset of patients with HADS-anxiety or HADS-depression subscale scores ≥8 at baseline (the cut-off value for anxiety or depression), a larger proportion of patients

in the Dupixent® 300 mg Q2W + TCS and 300 mg QW + TCS groups achieved HADS-anxiety and HADS-depression scores <8 at week 52 compared to placebo + TCS (See Table 5).

**Table 5: Other Secondary Endpoint Results of Dupixent® with Concomitant TCS at Week 16 and Week 52 in CHRONOS**

| | **Concomitant Use of TCS** | | | | | |
|---|---|---|---|---|---|---|
| | **CHRONOS at Week 16** | | | **CHRONOS at Week 52** | | |
| | **Placebo** | **'TM' 300 mg Q2W + TCS** | **'TM' 300 mg QW + TCS** | **Placebo +TCS** | **'TM' 300 mg Q2W + TCS** | **'TM' 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, % | | | | | | |
| ***Number of patients with DLQI ≥4 at baseline*** | 300 | 100 | 311 | 254 | 85 | 264 |

LS = least squares; SE = standard error

[a] p-value <0.0001

[b] p-value <0.001

[c] p-value <0.05

## PHARMACOKINETICS

### ABSORPTION

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

Administration of a single loading dose on Day 1 leads to rapid attainment of clinically effective concentrations within 2 weeks.

For every other week dosing (Q2W) with 300 mg, starting with a respective loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 10 weeks in a typical patient. Mean steady state trough concentration was 74 mg/L.

For weekly dosing (QW) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 13 weeks in a typical patient. Mean steady state trough concentration was 189 mg/L.

**Dose 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.

### 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.

### METABOLISM

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-4Rα target-mediated elimination predominates.

After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, determined by population PK analysis, was 10 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

### SPECIAL POPULATIONS

**Gender**

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

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

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

**Pediatric patients**
The pharmacokinetics of dupilumab in pediatric patients have not been studied.

**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. No data are available in patients with severe renal impairment.

**Body weight**
No dose adjustment for body weight is recommended.

**NON-CLINICAL SAFETY DATA**
Dupilumab does not adequately interact with the non-human IL-4Rα of animals typically utilized for the preclinical assessment of toxicology, pregnancy, lactation or fertility. Therefore, some of these assessments were conducted using surrogate antibodies against the IL-4Rα of monkeys and mice.

**ANIMAL PHARMACOLOGY**
Dupilumab binds with high affinity to human IL-4Rα and inhibits both IL-4 and IL-13 mediated signaling in vitro and in vivo. Administration of dupilumab leads to a reduction in type 2 (including Th2) inflammation in different mouse models using mice that express human IL-4Rα and human IL-4. In the house dust mite (HDM) allergen inflammation model, dupilumab decreases circulating levels of IgE and allergen-specific IgG1, reduces pulmonary infiltration of eosinophils, and reduces goblet cell metaplasia in this model of type 2 (including Th2)-driven inflammation.

**ACUTE TOXICITY**
No single-dose toxicology studies were conducted.

**CHRONIC TOXICITY**
No dose-limiting or target organ toxicity was observed in repeat-dose toxicology studies up to 5 weeks duration in mice and 6 months duration in cynomolgus monkeys conducted with surrogate antibodies. The no-observed-adverse-effect-level (NOAEL) was the highest dose administered in these studies (200 mg/kg/week in mice and 100 mg/kg/week in monkeys). Serum drug levels achieved at these dosages were

sufficient to have fully saturated the IL-4Rα in both species.

No adverse effects were observed in monkeys using a surrogate antibody against IL-4Rα when administered subcutaneously at doses up to 100 mg/kg/week for 26 weeks. No juvenile toxicology studies have been conducted with dupilumab or any of its surrogates.

**CARCINOGENICITY**
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 risk of cancer for dupilumab.

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

**GENOTOXICITY**
No genotoxicity studies were conducted.

**TERATOGENICITY**
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. The overall rate of embryofetal loss during gestation was 5 of 20 (25%) in control animals, 10 of 20 (50%) in animals treated with 25 mg/kg/week, and 3 of 18 (17%) in animals treated with 100 mg/kg/week. The exposure at 25 mg/kg/week or greater was at least 5-fold above the concentration needed to saturate the IL-4Rα receptors.

The rate of embryofetal loss observed in control animals from other studies conducted at the laboratory ranged from 7% to 39%. Concentrations of the surrogate antibody observed in the infant monkeys at birth were comparable to those observed in maternal serum, indicating that the surrogate antibody, like other IgG antibodies, crosses the placental barrier. There were no adverse effects of the surrogate antibody on maternal monkeys dosed with up to 100 mg/kg/week (the highest dosage administered). Serum drug levels achieved during this study were sufficient to fully saturate the IL-4Rα in monkeys at all doses.

An enhanced pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with a surrogate antibody against IL-4Rα, at doses up to 100 mg/kg/week once weekly for approximately 21 weeks, from approximately gestational day 20 through natural birth. There were no adverse effects in maternal animals or their offspring up to 6 months post-partum/post-birth. Drug levels achieved during this study were sufficient to fully saturate the IL-4Rα in monkeys. Measurable concentrations of the monkey surrogate antibody in serum were observed in infant monkeys, indicating that this antibody, like other IgG antibodies, crosses the placental barrier. The no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity was considered to be 100 mg/kg/week, the highest administered dose.

**IMPAIRMENT OF FERTILITY**
Fertility studies conducted in male and female mice using a surrogate antibody against IL-4Rα showed no impairment of fertility. The no-observed-effect-level (NOEL) was the maximum dose studied, 200 mg/kg/week administered subcutaneously.

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

**STORAGE CONDITIONS AND SHELF-LIFE**

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
Do not freeze
Do not expose to heat
Do not shake.
Do not use beyond the expiry date stamped on the carton and container label.

**PREPARATION AND HANDLING**
The patient may either self -inject Dupixent®, or a caregiver may administer Dupixent®, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If the solution is discolored or contains visible particulate matter, the solution should not be used.

The 300 mg pre-filled syringe with a needle shield or pre-filled syringe should be allowed to reach room temperature by waiting for 45 min before injecting Dupixent®.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C (77°F) for a maximum of 14 days. Do not store above 25°C (77°F). After removal from the refrigerator, Dupixent® must be used within 14 days or discarded.

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

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

**Manufactured by:**
**Sanofi Winthrop Industrie**
1051 Boulevard Industriel,
Le Trait (France) – 76580

**Importer:**
**Sanofi Healthcare India Private Limited,**
Gala No.4, Ground Floor, Building No Bl,
City Link Warehousing Complex,
S No. 121/ 10/A,121/10/B And 69,
NH3 Vadape, Tai- Bhiwandi 16, Thane Z5, Bhiwandi,
Maharashtra (India) - 421302.

Reference: Dupilumab CCDS, Version 3.0 dated 16th June 2017
Update: August 2023

**Instructions for use**

# Dupilumab 150 mg/ml solution for Injection

**DUPIXENT®**

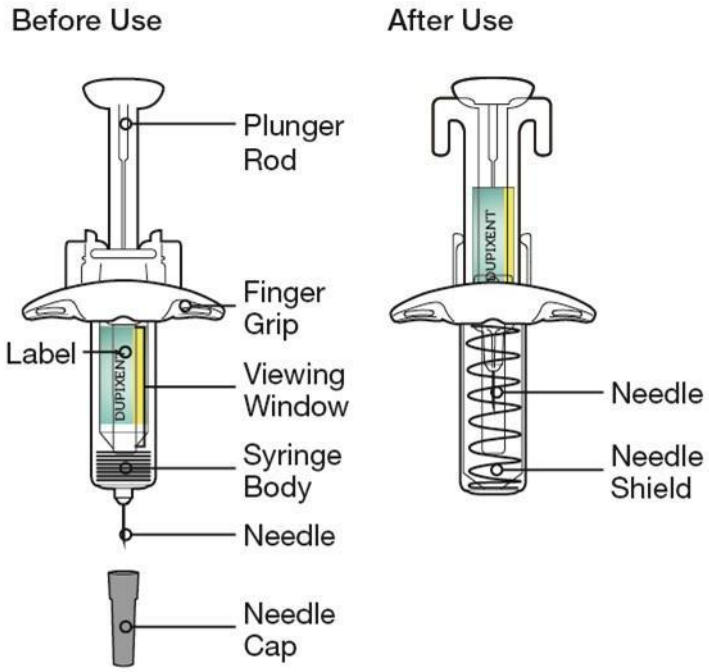
Pre-filled syringe with needle shield

**Read the instructions for Use before using the Dupixent® Prefilled Syringe**

This device is a single dose pre-filled syringe (called syringe in these instructions). It contains 300mg of Dupixent® for injection under the skin (subcutaneous injection).

Keep these instructions for future use. Any further questions? Ask your healthcare provider.

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




**Important information**

It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.

- 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.
- Rotate the injection site for each time you inject.
- **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 reduce the risk of accidental needle sticks, each pre-filled syringe has a needle shield that

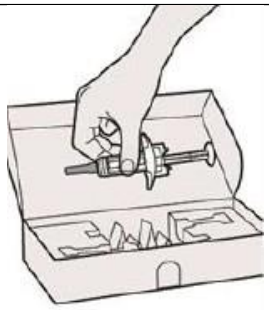
is automatically activated to cover the needle after you have given your injection.

- **Do not** pull back on the plunger rod at any time.
- **Do not** re-use the syringe.

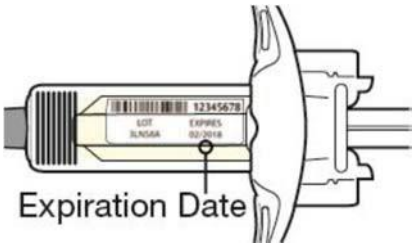
**How to Store Dupixent®**

- 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.
- Remove the syringe from the refrigerator at least 45 minutes before your injection so that it reaches room temperature.
- **Do not** keep Dupixent® at room temperature for more than 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.<br><br>**Do not pull off the Needle Cap until you are ready to inject.**<br><br>**Do not use the Syringe if it has been dropped on a hard surface or damaged.** |  |

**Step 2 Prepare**

| | |
|---|---|
| Ensure you have the following:<br>• the Dupixent® Pre-filled Syringe<br>• 1 alcohol wipe*<br>• 1 cotton ball or gauze*<br>• *<a puncture-resistant container>** (See Step 12)<br>** Items not included in the carton*<br><br>Look at the label:<br>• Check the expiration date.<br>• Check that you have the correct product and dose.<br><br>**Do not use the Syringe if the expiration date has passed.** |  |

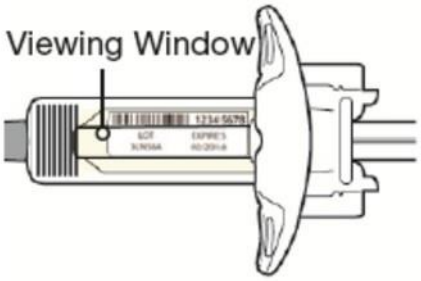
**Step 3 Inspect**

Look at the medicine through the Viewing Window on the Syringe:

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

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

**Do not use the Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**



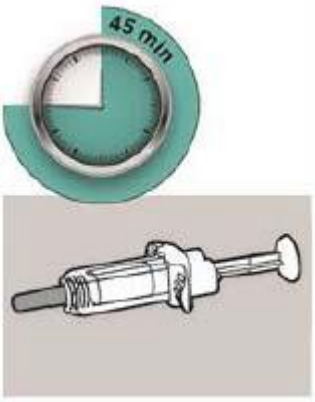

**Step 4 Wait 45 Minutes**

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

**Do not heat the Syringe.**

**Do not put the Syringe into direct sunlight.**

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

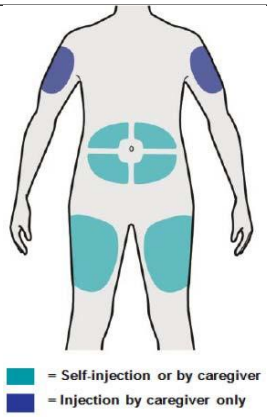



**Step 5 Choose**

Select the injection site.

- You can inject into your thigh or stomach, except for the 2 inches (5 cm) around your navel.
- If somebody else gives you the injection, you can also use the upper

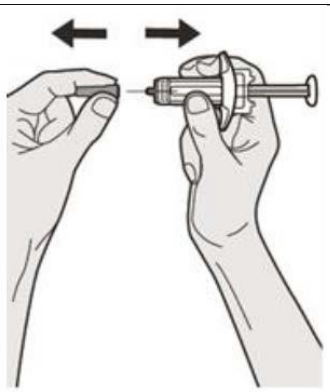
**Do not inject into skin that is tender, damaged or has bruises or scars.**



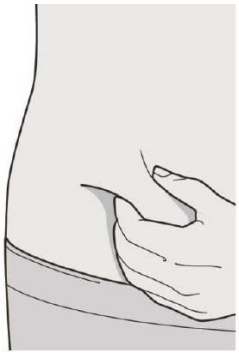
**Step 6 Clean**

| | |
|---|---|
| Wash your hands.<br>Clean the injection site with an alcohol wipe.<br>Let your skin dry before injecting.<br><br>**Do not touch the injection site again or blow on it before the injection.** |  |

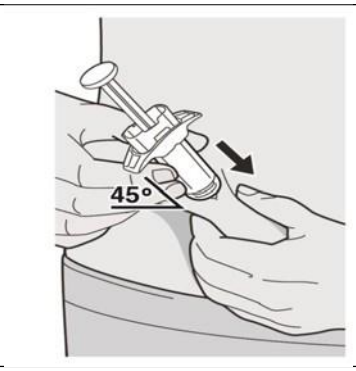
**Step 7 Pull**

| | |
|---|---|
| Hold the Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.<br><br>**Do not put the Needle Cap back on.**<br><br>**Do not touch the Needle.**<br><br>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. |  |

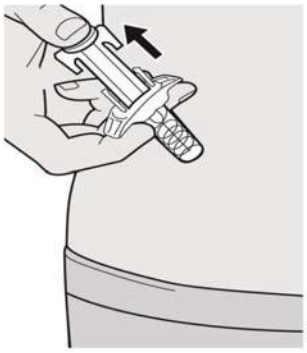
**Step 9 Insert**

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

**Step 10 Push**

| | |
|---|---|
| Relax the pinch.<br>Push the Plunger Rod down slowly and steadily as far as it will go until the Syringe is empty.<br><br>*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.<br>Lightly press a cotton ball or gauze on the injection site if you see any blood.<br><br>**Do not put the Needle Cap back on.**<br><br>**Do not rub your skin after the injection.** |  |

**Step 12 Dispose**

| | |
|---|---|
| Dispose of the Syringe and the Needle Cap in a puncture-resistant container.<br><br>**Do not put the Needle Cap back on.**<br><br>Always keep the container out of the reach of children. |  |

**Manufactured by:**
**Sanofi Winthrop Industrie**
1051 Boulevard Industriel, Le Trait (France) – 76580

**Importer:**
**Sanofi Healthcare India Private Limited,**
Gala No.4, Ground Floor, Building No Bl,
City Link Warehousing Complex,
S No. 121/ 10/A,121/10/B And 69,
NH3 Vadape, Tal- Bhiwandi 16, Thane Z5, Bhiwandi,
Maharashtra (India) - 421302.

Reference: Dupilumab Company Core Device Manual, Version 4 dated 11 December 2017
Update: August 2023