

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist 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. DUPIXENT can be used with or without topical corticosteroids. (1)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2.1)
- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity:** If a systemic hypersensitivity reaction occurs, discontinue DUPIXENT immediately and initiate appropriate therapy. (5.1)
- Conjunctivitis and Keratitis:** Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- Comorbid Asthma:** Advise patients with comorbid asthma not to adjust or stop their asthma treatment without consultation with their physicians. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 1\%$) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-387-4936 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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. DUPIXENT can be used with or without topical corticosteroids.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

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.

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

If a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

2.2 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".

For the initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

Administer subcutaneous injection into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. The upper arm can also be used if a caregiver administers the injection.

Rotate the injection site with each injection. DO NOT inject DUPIXENT into skin that is tender, damaged, bruised, or scarred.

The DUPIXENT "Instructions for Use" contains more detailed instructions on the preparation and administration of DUPIXENT [*see Instructions for Use*].

2.3 Preparation for Use of DUPIXENT Pre-filled Syringe With Needle Shield

Before injection, remove DUPIXENT pre-filled syringe from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes) without removing the needle cap.

Inspect DUPIXENT visually for particulate matter and discoloration prior to administration. DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution. Do not use if the liquid contains visible particulate matter, is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). DUPIXENT does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe.

3 DOSAGE FORMS AND STRENGTHS

DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2 mL in a single-dose pre-filled syringe with needle shield

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab [see *Adverse Reactions (6.2)*]. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see *Adverse Reactions (6.1, 6.2)*].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period [see *Adverse Reactions (6.1)*].

Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period [see *Adverse Reactions (6.1)*].

Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Comorbid Asthma

Safety and efficacy of DUPIXENT have not been established in the treatment of asthma. Advise patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.4 Parasitic (Helminth) Infections

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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity [*see Warnings and Precautions (5.1)*]
- Conjunctivitis and Keratitis [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4):

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 1: Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

| Adverse Reaction | DUPIXENT Monotherapy ^a | | DUPIXENT + TCS ^b | |
|---|-----------------------------------|----------------|--|----------------|
| | DUPIXENT 300 mg Q2W ^c | Placebo | DUPIXENT 300 mg Q2W ^c + TCS | Placebo + TCS |
| | N=529 n (%) | N=517 n (%) | N=110 n (%) | N=315 n (%) |
| Injection site reactions | 51 (10) | 28 (5) | 11 (10) | 18 (6) |
| Conjunctivitis ^d | 51 (10) | 12 (2) | 10 (9) | 15 (5) |
| Blepharitis | 2 (<1) | 1 (<1) | 5 (5) | 2 (1) |
| Oral herpes | 20 (4) | 8 (2) | 3 (3) | 5 (2) |
| Keratitis ^e | 1 (<1) | 0 | 4 (4) | 0 |
| Eye pruritus | 3 (1) | 1 (<1) | 2 (2) | 2 (1) |
| Other herpes simplex virus infection ^f | 10 (2) | 6 (1) | 1 (1) | 1 (<1) |
| Dry eye | 1 (<1) | 0 | 2 (2) | 1 (<1) |

^a pooled analysis of Trials 1, 2, and 4

^b analysis of Trial 3 where subjects were on background TCS therapy

^c DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks

^d Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

^e Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

^f Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3):

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Specific Adverse Reactions

Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years) [see [Warnings and Precautions \(5.2\)](#)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups.

Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + TCS trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, and generalized urticaria [see [Contraindications \(4\)](#), [Warnings and Precautions \(5.1\)](#), and [Adverse Reactions \(6.2\)](#)].

Eosinophils

DUPIXENT-treated subjects had a greater mean initial increase from baseline in eosinophil count compared to subjects treated with placebo in the monotherapy trials. Eosinophil counts declined to near baseline levels by Week 16. The initial increase in eosinophils was not observed in the 52-week DUPIXENT + TCS trial.

In Trials 1, 2, and 3, the incidence of treatment-emergent eosinophilia (≥ 500 cells/mcL) was similar in DUPIXENT and placebo groups. In Trials 1, 2, and 3, treatment-emergent eosinophilia ($\geq 5,000$ cells/mcL) was reported in <1% of DUPIXENT-treated patients and none in placebo-treated patients. In most cases, eosinophil counts declined to near baseline during study treatment.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing 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. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 7% of subjects with atopic dermatitis who received DUPIXENT 300 mg Q2W for 16 weeks developed antibodies to dupilumab. Of the subjects who developed antibodies to dupilumab, approximately 30% (2% of all subjects receiving DUPIXENT) had antibodies that were classified as neutralizing.

Of the subjects with atopic dermatitis who received DUPIXENT 300 mg Q2W + TCS for 52 weeks, approximately 7% developed antibodies to dupilumab and approximately 2% had persistent antibody responses, defined as having at least 2 consecutive positive post-baseline samples. Of the subjects

who developed antibodies to dupilumab, approximately 14% (1% of all subjects receiving DUPIXENT + TCS) had antibodies that were classified as neutralizing.

In subjects who received DUPIXENT, development of antibodies to dupilumab was associated with lower serum dupilumab concentrations [see *Clinical Pharmacology (12.3)*].

Antibodies to dupilumab were detected in approximately 2% and 8% of subjects with atopic dermatitis in the placebo or the placebo + TCS groups, respectively.

The antibody titers detected in both DUPIXENT and placebo subjects were generally low. Two subjects developed serum sickness or serum sickness-like reactions and high titers of antibodies to dupilumab during DUPIXENT therapy [see *Warnings and Precautions (5.1)*].

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel[®]) and a meningococcal polysaccharide vaccine (Menomune[®]). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on DUPIXENT use in pregnant women to inform any drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4R α) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) [see *Data*]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4R α up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy in pediatric patients (<18 years of age) have not been established.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects [*see Clinical Pharmacology (12.3)*].

10 OVERDOSE

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

11 DESCRIPTION

Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4R α subunit and inhibits IL-4 and IL-13 signaling. Dupilumab has an approximate molecular weight of 147 kDa.

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

DUPIXENT (dupilumab) Injection 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 pre-filled syringe with needle shield in a 2.25 mL siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex. Each pre-filled syringe delivers 300 mg dupilumab in 2 mL which also contains L-arginine hydrochloride (10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4R α subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Blocking IL-4R α with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE.

12.2 Pharmacodynamics

Consistent with receptor blockade, serum levels of IL-4 and IL-13 were increased following dupilumab treatment. The relationship between the pharmacodynamic activity and the mechanism(s) by which dupilumab exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, dupilumab reached peak mean \pm SD concentrations (C_{\max}) of 70.1 ± 24.1 mcg/mL by approximately 1 week post dose.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or every other week. Across clinical trials, the mean \pm SD steady-state trough concentrations ranged from 73.3 ± 40.0 mcg/mL to 79.9 ± 41.4 mcg/mL for 300 mg administered every 2 weeks and from 173 ± 75.9 mcg/mL to 193 ± 77.0 mcg/mL for 300 mg administered weekly.

The bioavailability of dupilumab following a SC dose is estimated to be 64%.

Distribution

The estimated total volume of distribution was approximately 4.8 ± 1.3 L.

Elimination

The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W or 300 mg QW dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10 and 13 weeks, respectively.

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25-times to 2-times the recommended dose).

Weight

Dupilumab trough concentrations were lower in subjects with higher body weight.

Immunogenicity

Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. A few subjects who had high antibody titers also had no detectable serum dupilumab concentrations.

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean \pm SD steady-state trough concentrations of dupilumab were 69.4 ± 31.4 mcg/mL and 166 ± 62.3 mcg/mL, respectively, for 300 mg administered every 2 weeks and weekly. No dose adjustment in this population is recommended.

Renal or Hepatic Impairment

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted.

Drug Interaction Studies

Cytochrome P450 Substrates

The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in a study with 12-13 evaluable subjects with atopic dermatitis (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature mice that were subcutaneously administered a homologous antibody against IL-4R α at doses up to 200 mg/kg/week.

14 CLINICAL STUDIES

Three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an 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 involvement of $\geq 10\%$. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (Trials 1 and 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the peak pruritus NRS from baseline to Week 16.

Clinical Response at Week 16 (Trials 1, 2, and 3)

The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 2.

Table 2: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS)

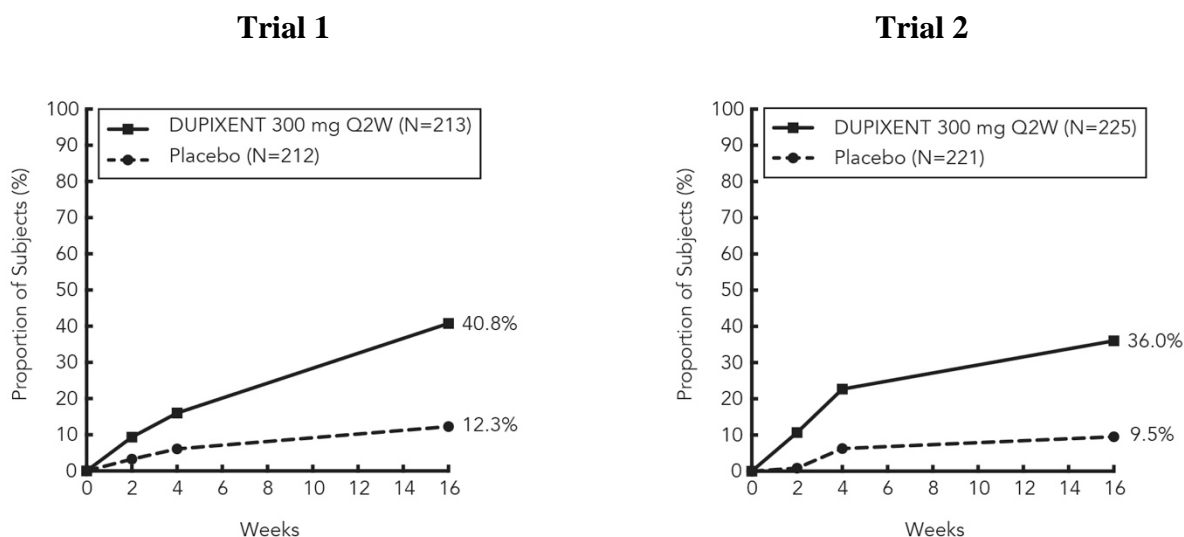
| | Trial 1 | | Trial 2 | | Trial 3 | |
|---|---------------------|---------|---------------------|---------|---------------------------|---------------|
| | DUPIXENT 300 mg Q2W | Placebo | DUPIXENT 300 mg Q2W | Placebo | DUPIXENT 300 mg Q2W + TCS | Placebo + TCS |
| Number of subjects randomized (FAS) ^a | 224 | 224 | 233 | 236 | 106 | 315 |
| IGA 0 or 1 ^{b,c} | 38% | 10% | 36% | 9% | 39% | 12% |
| EASI-75 ^c | 51% | 15% | 44% | 12% | 69% | 23% |
| EASI-90 ^c | 36% | 8% | 30% | 7% | 40% | 11% |
| Number of subjects with baseline Peak Pruritus NRS score ≥ 4 | 213 | 212 | 225 | 221 | 102 | 299 |
| Peak Pruritus NRS (≥ 4 -point improvement) ^c | 41% | 12% | 36% | 10% | 59% | 20% |

^a Full Analysis Set (FAS) includes all subjects randomized.

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

Figure 1: Proportion of Subjects with ≥ 4 -point Improvement on the Pruritus NRS in Trial 1^a and Trial 2^a Studies (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 randomized.

In Trial 3, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment (e.g., 24% of DUPIXENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 3.

Table 3: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52

| | DUPIXENT 300 mg Q2W + TCS | Placebo + TCS |
|---|--------------------------------------|----------------------|
| Number of Subjects ^a | 89 | 264 |
| Responder ^{b,c} at Week 16 and 52 | 22% | 7% |
| Responder at Week 16 but Non-responder at Week 52 | 20% | 7% |
| Non-responder at Week 16 and Responder at Week 52 | 13% | 6% |
| Non-responder at Week 16 and 52 | 44% | 80% |
| Overall Responder ^{b,c} Rate at Week 52 | 36% | 13% |

^a In Trial 3, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.

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

Treatment effects in subgroups (weight, age, gender, race, and prior treatment, including immunosuppressants) in Trials 1, 2, and 3 were generally consistent with the results in the overall study population.

In Trials 1, 2, and 3, a third randomized treatment arm of DUPIXENT 300 mg QW did not demonstrate additional treatment benefit over DUPIXENT 300 mg Q2W.

Subjects in Trials 1 and 2 who had an IGA 0 or 1 with a reduction of ≥ 2 points were re-randomized into Trial 5. Trial 5 evaluated multiple DUPIXENT monotherapy dose regimens for maintaining treatment response. The study included subjects randomized to continue with DUPIXENT 300 mg Q2W (62 subjects) or switch to placebo (31 subjects) for 36 weeks. IGA 0 or 1 responses at Week 36 were as follows: 33 (53%) in the Q2W group and 3 (10%) in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield. Each pre-filled syringe with needle shield is designed to deliver 300 mg of DUPIXENT in 2 mL solution.

DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield.

| | |
|--------------------|--|
| Pack Size | 300 mg/2 mL Pre-filled Syringe with Needle Shield |
| Pack of 2 syringes | NDC 0024-5914-01 |

16.2 Storage and Handling

DUPIXENT is sterile and preservative-free. Discard any unused portion.

Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.

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

Do not expose the syringe to heat or direct sunlight.

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

Do NOT freeze. Do NOT expose to heat. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations [see *Instructions for Use*].

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions [see *Warnings and Precautions (5.1)*].

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see *Warnings and Precautions (5.2)*].

Comorbid Asthma

Advise patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see *Warnings and Precautions (5.3)*].

REGENERON

SANOFI GENZYME 

Manufactured by:

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY 10591

U.S. License No. 1760

Marketed by:

sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

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