▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - DUPIXENT®

1 NAME OF THE MEDICINE

AUSTRALIAN APPROVED NAME

Dupilumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe is designed to deliver 300 mg dupilumab in 2 mL (150 mg/mL solution). It is supplied as a single-use pre-filled syringe with or without needle shield.

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.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Dupixent is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection which is free from visible particulates.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for chronic systemic therapy. Dupixent is not intended for episodic use.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dupixent treatment should be initiated and supervised by a dermatologist or immunologist.

The recommended dose of Dupilumab for adult patients is as follows:

- Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites), followed by 300 mg given every other week.

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

Product is for single use in one patient only. Discard any residue.

SPECIAL POPULATIONS

Paediatric patients

Safety and efficacy in paediatric patients have not been established (see 5.2 PHARMACOKINETIC PROPERTIES).

Elderly patients

No dose adjustment is recommended for elderly patients (see 5.2 PHARMACOKINETIC PROPERTIES)

Hepatic impairment

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

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 (see 5.2 PHARMACOKINETIC PROPERTIES).

Body weight

No dose adjustment for body weight is recommended.

PREPARATION AND HANDLING

Before injection, remove Dupixent pre-filled syringe from the refrigerator and allow to reach room temperature by waiting for 45 min 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.

Comprehensive instructions for administration are given in the package leaflet.

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

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

Any unused medicinal product or waste material should be disposed. A puncture-resistant container for disposal of syringes should be used and should be kept out of the reach of children.

ADMINISTRATION

Dupixent is intended for use under the guidance of a healthcare provider. The patient's caregiver may administer Dupixent or the patient may self-inject it after guidance has been provided by a healthcare professional on proper subcutaneous injection technique. Provide proper training to patients and/or caregivers on the preparation and administration of Dupixent prior to use according to the instruction leaflet inside the pack.

Administer subcutaneous injection into the thigh or abdomen, except for the 5 cm (2 inches) around the navel, using a single-dose pre-filled syringe. If somebody else administers the injection, the upper arm can also be used. Rotate the injection site with each injection.

DO NOT inject Dupixent into skin that is tender, damaged or has bruises or scars.

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

4.3 CONTRAINDICATIONS

Dupixent is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve the traceability of biological medicines, the tradename and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.

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 (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Both cases were associated with high titers of ADA to dupilumab.

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.

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 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) 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 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

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.

Concomitant Atopic Conditions

Safety and efficacy have not been established in allergic or atopic conditions other than atopic dermatitis. Patients with comorbid atopic conditions (such as 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.

Use in the elderly

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

Paediatric Use

Safety and efficacy in paediatric patients have not been established.

Effects on laboratory tests

There is no known interference between Dupixent and routine laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Live Vaccines

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

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) and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

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

Interactions with CYP450 Substrates

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

Other

There are no data on the safety of Dupixent when co-administered with other immunomodulators .

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 which yielded a high multiple of the exposure (serum AUC) in patients at the recommended dose.

Use in pregnancy (Category B1)

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. Like other IgG antibodies, dupilumab is expected to cross the placental barrier.

In an enhanced pre-and postnatal development study, pregnant cynomolgus monkeys were administered a surrogate antibody against IL-4Rα by subcutaneous injection once weekly at doses up to 100 mg/kg/week, from the beginning of organogenesis to parturition. The surrogate antibody used displayed considerably lower affinity for monkey IL-4Rα compared to dupilumab for human IL-4Rα, but the doses used in the study were sufficient to saturate maternal IL-4Rα receptors throughout the treatment period. No treatment-related effects on embryofetal survival, malformations, or on growth, functional development or immunology were observed in the offspring, monitored from birth through to 6 months of age.

Use in lactation

There are no specific data on the presence of dupilumab in human milk. But human IgG is known to 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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%), food allergy (37%), 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%).

The adverse reactions in the following table are listed by system organ class and frequency using the following convention: Very common > 10%; Common > 1 and < 10%; Uncommon > 0.1 and < 1%, Rare > 0.01 and <0.1%; Very rare <0.01%; Not known *(cannot be estimated from available data).

Table 1 - List of adverse reactions in clinical studies[a]

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Conjunctivitis (4.0 %)
		Oral herpes (3.8%)
		Conjunctivitis bacterial (1.9%)
		Herpes simplex[b] (1.7 %)
Blood and lymphatic system disorders	Common	Eosinophilia (1.7%)
Eye disorders	Common	Conjunctivitis allergic (7.0%)
		Eye pruritus (2.9 %)
		Blepharitis (4.5%)
		Dry eye (1.8 %)
General disorders and administration site conditions	Very common	Injection site reactions (15.9 %)

System Organ Class	Frequency	Adverse Reaction

[a] Pooled data from placebo-controlled monotherapy clinical studies (SOLO 1, SOLO 2, and a phase 2, dose-ranging study data) and placebo-controlled concomitant therapy with TCS study (CHRONOS) in AD, patients exposed to 300 mg every other week or 300 mg once weekly with or without topical corticosteroids, up to 16 weeks

[b] 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 numerically lower in patients treated with 'TM' compared to placebo.

Table 4 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 3 - Adverse Reactions Occurring in ≥1% of Patients with Atopic Dermatitis Treated with Dupixent through Week 16 in Placebo-controlled Trials

Adverse Reaction	Dupixent[a] Monotherapy			Dupixent[b] + TCS		
	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 SOLO 1, SOLO 2, and a phase 2, dose-ranging study

b Safety Data from CHRONOS. 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 numerically 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 (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 3). 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. Overall, 0.7% of patients 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 (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

4.9 OVERDOSE

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

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

For information on the management of overdose, contact the Australian Poison Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 Effects

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 CHRONOS (87.0% and 84.9% of patients in the Dupixent 300 mg every two week dosing (Q2W) and 300 mg weekly dosing (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 receiving placebo. Similar trends were observed with antigen-specific IgEs such as those against S. aureus specific enterotoxin A, grass and tree allergens.

Clinical trials

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, Study 1334, (SOLO 1), Study 1416 (SOLO 2), and Study 1224 (CHRONOS) 2119 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3, an Eczema Area and Severity Index (EASI) score ≥16, and a minimum body surface area (BSA) involvement of ≥10%. Eligible patients enrolled into the three studies had previous inadequate response to topical medication.

In all three studies, patients received

1. an initial dose of 600 mg Dupixent (two 300 mg injections) on day 1, followed by 300 mg once every 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.

- Study 1334 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.
- Study 1416 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.
- Study 1224) 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") and 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 Study 1224, 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 (Study 1334 and Study 1416), 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

In the concomitant TCS study (Study 1224), 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.

Clinical Response

16-Week Monotherapy Studies (Study 1334 and Study 1416)

In Study 1334 and Study 1416, 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 1).

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 Study 1334 and 7.2%, 30%, and 30.5% of patients, respectively in Study 1416.

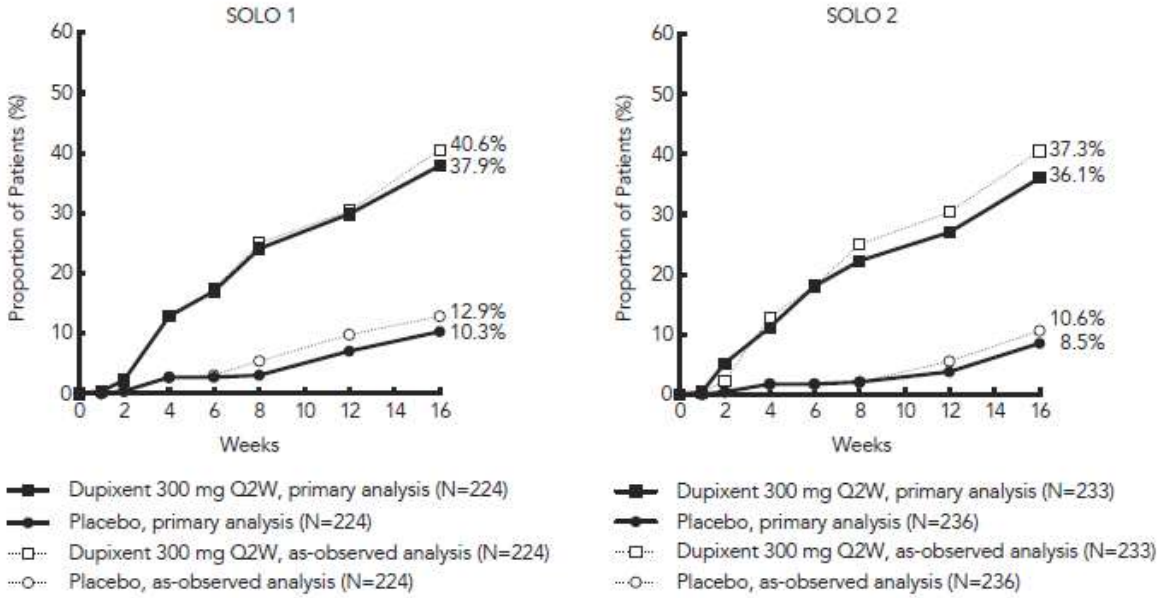
EASI-50 response at Week 16 was achieved 24.6% of patients in the placebo group, 68.8% in the Dupixent 300 mg Q2W group, and 61.0% in the Dupixent 300 mg QW group, respectively in Study 1334 and 22%, 65.2%, and 61.1% of patients, respectively in Study 1416.

Table 2 - Efficacy Results of Dupixent Monotherapy at Week 16 (FAS)

	Study 1334 (FAS)a			**Study 1416 (FAS)a**		
	Placebo	**Dupixent 300 mg Q2W**	**Dupixent 300 mg QW**	**Placebo**	**Dupixent 300 mg Q2W**	**Dupixent 300 mg QW**
Patients randomized	224	224	223	236	233	239
IGA 0 or 1[b], % responders[c]	10.3 %	37.9 %*	37.2 %*	8.5%	36.1 %*	36.4 %*
EASI-75, % responders[c]	14.7 %	51.3 %*	52.5 %*	11.9 %	44.2 %*	48.1 %*
EASI, LS mean % change from baseline (+/- SE)	-37.6% (3.28)	-72.3 % * (2.63)	-72.0 %* (2.56)	-30.9 % (2.97)	-67.1 % * (2.52)	-69.1 %* (2.49)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-26.1% (3.02)	-51.0%* (2.50)	-48.9* (2.60)	-15.4% (2.98)	-44.3%* (2.28)	-48.3* (2.35)
Number of patients with baseline pruritus NRS score≥ 4	212	213	201	221	225	228
Pruritus NRS (>4-point improvement), % responders[c, d]	12.3 %	40.8 %*	40.3 %*	9.5%	36.0 %*	39.0 %*

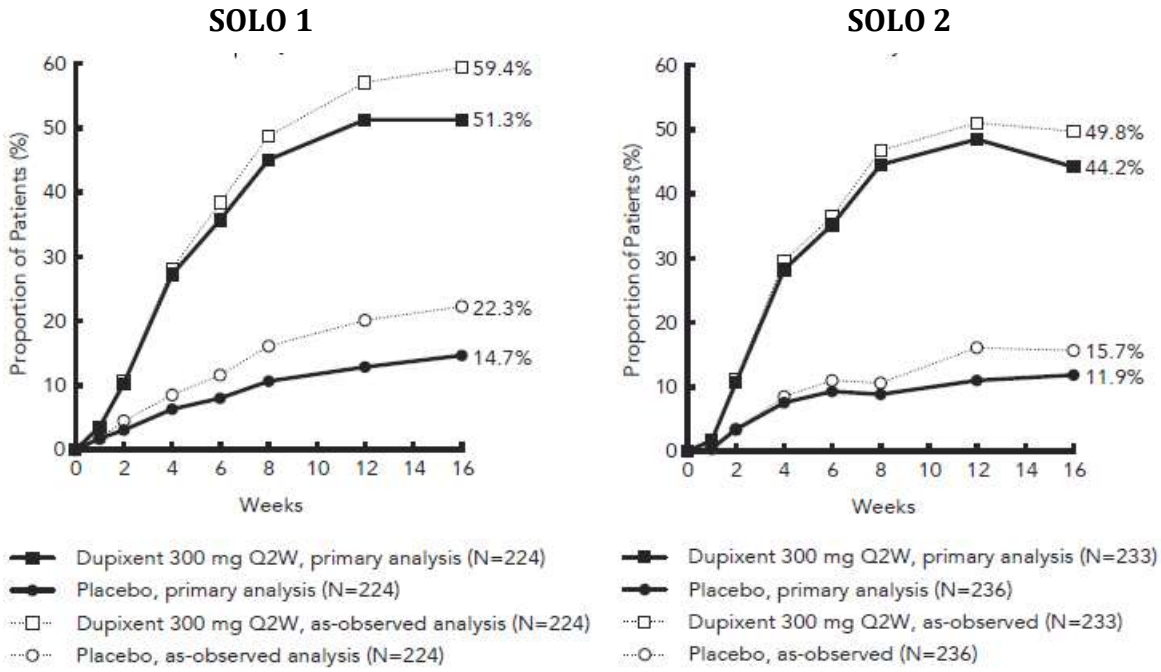
[a] Full analysis set (FAS) includes all patients randomized.
[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of > 2 points on a 0-4 IGA scale.
[c] Patients who received rescue treatment or with missing data were considered as non-responders.
[d] a significantly greater proportion of patients on Dupixent had improvement in pruritus NRS of ≥4 points compared to placebo at week 2 (p<0.01).
*p-value <0.0001
LS = least squares SE= standard error

Figure 1 - Proportion of Patients with IGA 0 or 1[a] in Study 1334 and Study 1416 (FAS)



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.
bIn 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.
cFull analysis set (FAS) includes all patients randomized.

Figure 2 - Proportion of Patients with EASI-75 in Study 1334 and Study 1416 (FASb)



[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 Study 1334 and Study 1416 were in general consistent with the results in the overall study population.

52-Week Concomitant TCS Study (Study 1224)

In Study 1224), 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 pruritis NRS from baseline to week 16 and week 52 compared to placebo + TCS (see Table 2).

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 Study 1224.

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 Study 1224 study at Week 52.

EASI-50 response was achieved 29.9% of patients in the placebo group, 70.7% in the Dupixent 300 mg Q2W group, and 70.0% in the Dupixent 300 mg QW group, respectively in Study 1224 at Week 52.

Table 3 - Efficacy Results of Dupixent with Concomitant TCS[a] at Week 16 and Week 52 in Study 1224

	Week 16 (FAS)[b]			**Week 52 (FAS Week 52)[b]**		
	Placebo + TCS	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**	**Placebo + TCS**	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**
Patients randomized	315	106	319	264	89	270

	Week 16 (FAS)[b]			Week 52 (FAS Week 52)[b]		
	Placebo + TCS	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**	**Placebo + TCS**	**Dupixent 300 mg Q2W + TCS**	**Dupixent 300 mg QW + TCS**
IGA 0 or 1[c], % responders [d]	12.4 %	38.7 %*	39.2 %*	12.5 %	36.0%*	40.0 %*
EASI-75, % responders [d]	23.2 %	68.9 %*	63.9 %*	21.6 %	65.2 %*	64.1 %*
EASI, LS mean % change from baseline (+/- SE)	-48.4 % (3.82)	-80.5 %* (6.34)	-81.5 %* (5.78)	-60.9 % (4.29)	-84.9 %# (6.73)	-87.8 % ‡ (6.19)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-30.3 (2.36)	-56.6* (3.95)	-57.1 (2.11)	-31.7 (3.95)	-57.0§ (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 %*	50.8 %*	12.9 %	51.2 %*	39.0 %*

* p-value <0.0001,
‡ p-value = 0.0003,
§ p-value = 0.0005,
# p-value = 0.0015

[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.

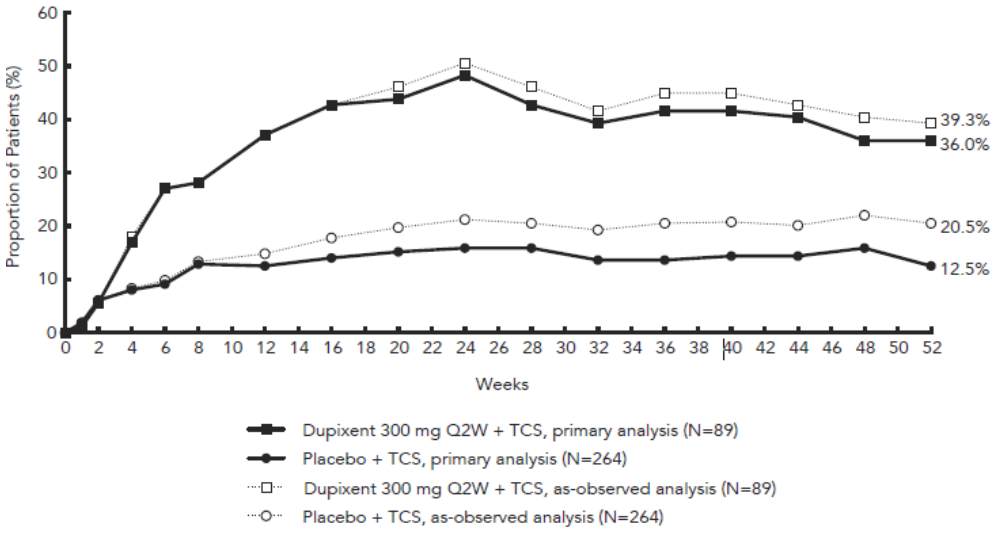
[c] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.

[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 ($p<0.05$).

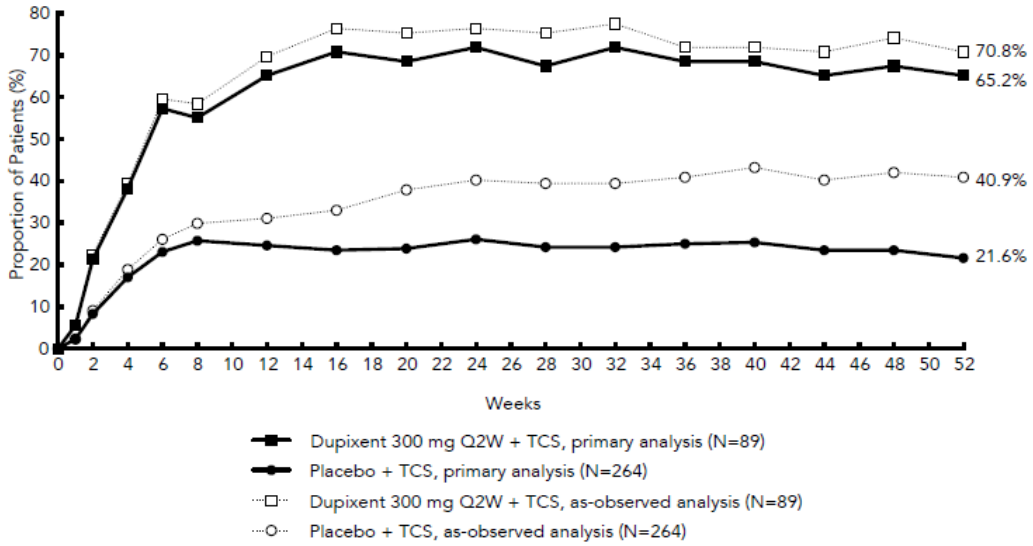
LS = least square SE = standard error

Figure 3 - Proportion of Patients with IGA 0 or 1a in Study 1224 (FAS Week 52[c])



[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) 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 EASI-75 in Study 1224 (FAS Week 52[b])



[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) 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 Study 1224 were in general consistent with the results in the overall study population.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Administration of a single loading dose of 600 mg 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 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.

Distribution

A volume of distribution for dupilumab of approximately 4.6L 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.

Excretion

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4R α target-mediated elimination predominates.

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

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.

Special Populations

Gender

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

Elderly

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

Race

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

Paediatric Patients

The pharmacokinetics of dupilumab in paediatric 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 Dupixent. No data are available in patients with severe renal impairment.

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY

No genotoxicity studies were conducted. As a monoclonal antibody, dupilumab is not expected to interact with DNA or other chromosomal material.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Arginine hydrochloride (25 mM), histidine (20 mM), polysorbate 80 (0.2% (w/v)), sodium acetate (12.5 mM), sucrose (5% (w/v)), and water for injections, adjusted to pH 5.9 with acetic acid.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the refrigerator at 2°C to 8°C in the original carton to protect from light. Do not freeze. Do not expose to heat. Do not shake.

Do not use after the expiry date stamped on the carton and container label.

6.5 NATURE AND CONTENTS OF CONTAINER

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. The needle cap is not made with natural rubber latex.

Dupixent is available in pack sizes of 1* or 2, 3* and 6* per carton in the following presentations.

- **Pre-filled Syringe**

- **Pre-Filled Syringe with needle shield** - the pre-filled syringe has a needle shield to reduce the risk of accidental needle stick injuries.

* Presentations currently not marketed

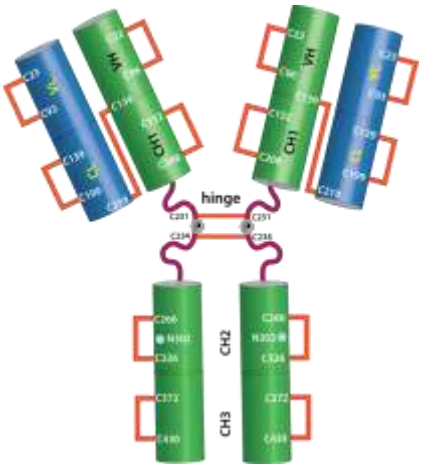
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine should be disposed of by taking to your local pharmacy. The syringe and the needle cap should be disposed of in a sharps container.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Dupixent 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) $G4^P$ isotype 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.



CAS number

1190264-60-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

AUSTRALIA
sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

NEW ZEALAND
sanofi-aventis new zealand limited
Level 8, James and Wells Tower
56 Cawley Street, Ellerslie,
Auckland
New Zealand

9 DATE OF FIRST APPROVAL

24 January 2018

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information