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

RECENT MAJOR CHANGES

Indications and Usage, Asthma (1.2) 10/2018
Dosage and Administration (2.2; 2.3; 2.4) 10/2018
Warnings and Precautions (5.1; 5.2; 5.3; 5.4; 5.5; 5.6; 5.7) 10/2018

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. (1.1)

• as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)

Limitations of Use
Not for the relief of acute bronchospasm or status asthmaticus (1.2)

DOSAGE AND ADMINISTRATION

• Administer by subcutaneous injection. (2)

Atopic Dermatitis

• 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)

Asthma

• The recommended dose of DUPIXENT for adults and adolescents (12 years of age and older) is:
  o an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
  o an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
  o for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week (2.2)

ADVERSE REACTIONS

Atopic Dermatitis: Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blenchitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)

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

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: 10/2018

DOSAGE FORMS AND STRENGTHS

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

• Injection: 200 mg/1.14 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: Hypersensitivity reactions (urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness) have occurred after administration of DUPIXENT. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)

• Conjunctivitis and Keratitis: Atopic Dermatitis: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)

• Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symp-
toms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)

• Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)

• Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treat-
ment, discontinue treatment with DUPIXENT until the infection resolves. (5.7)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

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.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection.

2.1 Atopic Dermatitis

The recommended dose of DUPLEXENT 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.

2.2 Asthma

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

- an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
- an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week

For patients with oral corticosteroids-dependent asthma, or with comorbid moderate-to-severe atopic dermatitis for which DUPLEXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week

2.3 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.

For the initial 400 mg dose, administer each of the two DUPIXENT 200 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.

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.

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

2.4 Preparation for Use of DUPLEXENT Pre-filled Syringe with Needle Shield

Before injection, remove DUPLEXENT pre-filled syringe from the refrigerator and allow DUPLEXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe and 30 minutes for the 200 mg/1.14 mL pre-filled syringe) without removing the needle cap.

Inspect DUPLEXENT visually for particulate matter and discoloration prior to administration. DUPLEXENT 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). DUPLEXENT does not contain preservatives, therefore, discard any unused product remaining in the pre-filled syringe.

3 DOSAGE FORMS AND STRENGTHS

DUPLEXENT 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
- Injection: 200 mg/1.14 mL in a single-dose pre-filled syringe with needle shield

4 CONTRAINDICATIONS

DUPLEXENT 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, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPLEXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis.[see Adverse Reactions (6.2)]. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPLEXENT.[see Adverse Reactions (6.1, 6.2)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPLEXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPLEXENT and placebo.[see Adverse Reactions (6.1)].

Keratitis was reported in less than 1% in the DUPLEXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPLEXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPLEXENT + 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. Among asthma subjects the frequency of keratitis was similar between DUPLEXENT and placebo.[see Adverse Reactions (6.1)].

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

5.3 Eosinophilic Conditions

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

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPLEXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPLEXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPLEXENT.

5.5 Reduction of Corticosteroid Dosage

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

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

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

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.

Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and a dose-ranging trial (Trial 4) evaluated the safety of DUPLEXENT 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 8% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 37% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPLEXENT, with or without concurrent topical corticosteroids (TCS). A total of 739 subjects were treated with DUPLEXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

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

Weeks 0 to 16 (Trials 1 to 4):

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

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPLEXENT 300 mg Q2W monotherapy groups, and in the DUPLEXENT + TCS group, all consistent with the respective comparator groups during the first 16 weeks of treatment.
Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Injection site reactions was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% following an initial dose of 400 mg or 600 mg, respectively.

‡ DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks
§ Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
† Keratitis includes keratitis, ulcerative keratitis, allergic keratitis, atomic keratoconjunctivitis, and ophthalmic herpes simples.
* Other herpes simplex virus infection cluster includes herpetic simplex, genital herpes, herpes simplex uterine, 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: atomic 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.

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) subjects who received DUPIXENT, development of high titer antibodies to dupilumab was less than 1% had neutralizing antibodies.

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to dupilumab. In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, and 3 (0.3%) of the placebo group.

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.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapy</th>
<th>DUPIXENT + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=529 n (%)</td>
<td>N=315 n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>51 (10)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Conjunctivitis 6</td>
<td>51 (10)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Blepharitis 2</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oral herpes 20 (4)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Keratitis 3 1 (&lt;1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Eye pruritus 3 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other herpes simplex virus infection 8</td>
<td>10 (2)</td>
<td></td>
</tr>
<tr>
<td>Dry eye 1 (&lt;1)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6 Month Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AS Trials 1 and 2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUPIXENT 200 mg Q2W</td>
<td>N=779 n (%)</td>
<td>N=517 n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Eosinophilia 7</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUPIXENT 300 mg Q2W</td>
<td>N=788 n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>144 (18%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Eosinophilia 7</td>
<td>17 (2%)</td>
</tr>
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</table>

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6 Month Safety Pool)

7.2 Non-Live Vaccines
Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were vaccinated 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 groups. The antibody titers detected in both DUPIXENT and placebo groups were mostly low. In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, and 3 (0.3%) of the placebo group.

7.3 Live Vaccines
Avoid use of live vaccines in patients treated with DUPIXENT.
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

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see Clinical Considerations). In an enhanced pre- and postnatal 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-4Rα) 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 populations are unknown. In a few pregnancies where a background risk of birth defects, 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.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preclampsia in the mother and premature, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In an enhanced pre- and postnatal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα 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 embryo-fetal 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. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure 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

Atopic Dermatitis

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

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. A total of 107 adolescents aged 12 to 17 years with severe asthma were enrolled in AS Trials 1 and 2. Subjects had a recent exacerbation of asthma within 60 days prior to dose. Both the 200 mg and 300 mg Q2W doses, improvements in FEV1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with placebo. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight [see Clinical Pharmacology (12.3)]. The adverse event profile in adolescents was generally similar to the adults [see Adverse Reactions (6.1)].

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 the two age groups, patients ages 65 and over is not sufficient to determine whether they respond differently from younger subjects [see Clinical Pharmacology (12.3)].

Of the 177 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

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 IgG subclass that binds to the IL-4Rα 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 siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg 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. Each 200 mg pre-filled syringe delivers 200 mg dupilumab in 1.14 mL, which also contains L-arginine hydrochloride (12 mg), L-histidine (3.5 mg), polysorbate 80 (2.3 mg), sodium acetate (1.2 mg), sucrose (57 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-4Rα 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.

Inflammation is an important component in the pathogenesis of asthma and atopic dermatitis. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eosinocoids, leukotrienes, cytokines, chemokines) are involved in inflammation.

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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-4Rα 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.

Inflammation is an important component in the pathogenesis of asthma and atopic dermatitis. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eosinocoids, leukotrienes, cytokines, chemokines) are involved in inflammation.

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 the two age groups, patients ages 65 and over is not sufficient to determine whether they respond differently from younger subjects [see Clinical Pharmacology (12.3)].

Of the 177 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

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-4Rα 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 siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.
Clinical Response at Week 16 (Trials 1, 2, and 3)

at least a 4-point improvement in the peak pruritus NRS from baseline to Week 16.

ment of at least 75% in EASI score from baseline), and reduction in itch as defined by improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant TCS trial (Trial 3) are presented in Table 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 3.

* Full Analysis Set (FAS) includes all subjects randomized.
† 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.
‡ Subjects who received rescue treatment or with missing data were considered as non-responders.

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 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 4.

| Table 3: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS) |
|-----------------|------------------|------------------|------------------|------------------|
|                  | Trial 1          | Trial 2          | Trial 3          |                  |
|                  | DUPIXENT         | Placebo          | DUPIXENT         | Placebo          |
|                  | 300 mg Q2W       |                  | 300 mg Q2W       |                  |
|                  |                  |                  |                  |                  |
| Number of subjects randomized (FAS) | 224 | 222 | 223 | 226 |
| Number of subjects with baseline Peak Pruritus NRS score ≥4 | 213 | 212 | 225 | 221 |
| Peak Pruritus NRS (≥4-point improvement)† | 41% | 12% | 36% | 10% |
| Placebo + TCS  | 59% | 20% | 59% | 20% |

* In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered as non-responders.

| Table 4: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52 |
|-----------------|------------------|------------------|------------------|
|                  | DUPIXENT         | Placebo          |                  |
|                  | 300 mg Q2W + TCS |                  |                  |
| Number of Subjects† | 264 |                  |                  |
| Responders† at Week 16 and 52 | 22% | 7% |
| Non-responders at Week 16 | 13% | 6% |
| Non-responders at Week 52 | 44% | 80% |
| Overall Responders† at Week 52 | 36% | 13% |

* In Trial 2 of the 421 randomized and treated subjects, 88 subjects (16%) had not been on study for 52 weeks at the time of data analysis.
† 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.
‡ 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.

<table>
<thead>
<tr>
<th>Table 2: Proportion of Subjects with ≥4-point Improvement on the Pruritus NRS in Trial 1 and Trial 2 (Studies FAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0-2</td>
</tr>
<tr>
<td>4-6</td>
</tr>
<tr>
<td>8-10</td>
</tr>
<tr>
<td>12-14</td>
</tr>
</tbody>
</table>

* In Trial 1 and Trial 2, 40 subjects each were randomized and treated with DUPIXENT 300 mg Q2W or Placebo.
† 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.
‡ Subjects who received rescue treatment or with missing data were considered as non-responders.

14.2 Asthma

The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in...
treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were excluded without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level >1500 cells/mL (<1.3%) were excluded. DUPIXENT was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1
AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate to severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV$_1$ (L) in subjects with baseline blood eosinophils ≥300 cells/mL. Other endpoints included percent change from baseline in FEV$_1$, and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥300 cells/mL and >300 cells/mL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2
AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 adolescent and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) DUPIXENT Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV$_1$. At Week 12 in the overall population (unrestricted by minimum baseline blood eosinophil counts), Additional secondary endpoints included annualized severe exacerbation rates and FEV$_1$ in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3
AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller. After completing the OCS dose during the screening period, subjects received 300 mg DUPIXENT (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their usual asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophil count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

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

Table 5: Demographics and Baseline Characteristics of Asthma Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial 1 (N=776)</th>
<th>Trial 2 (N=1902)</th>
<th>Trial 3 (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>49 (13)</td>
<td>48 (15)</td>
<td>51 (13)</td>
</tr>
<tr>
<td>% Female</td>
<td>63</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>% White</td>
<td>78</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>Duration of Asthma (years), mean (± SD)</td>
<td>22 (15)</td>
<td>21 (15)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>77</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Mean exacerbations in previous year (± SD)</td>
<td>2.2 (2.1)</td>
<td>2.1 (2.2)</td>
<td>2.1 (2.2)</td>
</tr>
<tr>
<td>High dose ICS use (%)</td>
<td>50</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>Pre-dose FEV$_1$ (L) at baseline (± SD)</td>
<td>1.84 (0.54)</td>
<td>1.78 (0.60)</td>
<td>1.58 (0.57)</td>
</tr>
<tr>
<td>Mean percent predicted FEV$_1$ at baseline (± SD)</td>
<td>61 (11)</td>
<td>58 (14)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>% Reversibility (± SD)</td>
<td>27 (15)</td>
<td>26 (22)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall (AD %, NP %, AR %)</td>
<td>73 (8, 11, 62)</td>
<td>78 (10, 13, 69)</td>
<td>72 (8, 21, 56)</td>
</tr>
<tr>
<td>Mean FeNO ppb (± SD)</td>
<td>39 (35)</td>
<td>35 (33)</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Mean total IgE IU/mL (± SD)</td>
<td>435 (754)</td>
<td>432 (747)</td>
<td>431 (776)</td>
</tr>
</tbody>
</table>

Table 6: Rate of Severe Exacerbations in AS Trials 1 and 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Trial 1</td>
<td>DUXIPENT 200 mg Q2W</td>
<td>0.30 (0.13, 0.68)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUXIPENT 200 mg Q2W</td>
<td>0.37 (0.29, 0.48)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Exacerbations
AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either DUXIPENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUXIPENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUXIPENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mL in AS Trials 1 and 2 are shown in Table 6.

Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 2. Prespecified subgroup analyses in AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥150 cells/mL. In subjects with baseline blood eosinophil count < 150 cells/mL, similar severe exacerbation rates were observed between DUXIPENT and placebo. In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency department visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUXIPENT 200 mg or 300 mg Q2W, respectively.
Improvements in FEV<sub>1</sub> blood eosinophil counts

DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to placebo.

Lung Function

Significant increases in pre-bronchodilator FEV<sub>1</sub> were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300 cells/mL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV<sub>1</sub>, LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥ 300 cells/mL in AS Trials 1 and 2 are shown in Table 7.

Improvements in FEV<sub>1</sub> by baseline blood eosinophils for AS Trial 2 are shown in Figure 4. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

**Table 7: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV<sub>1</sub> at Week 12 in AS Trials 1 and 2**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥ 300 cells/mL (primary analysis population, Trial 1)</th>
<th>N</th>
<th>LS Mean Change from baseline L (%)</th>
<th>LS Mean Difference vs. placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
<td>0.43 (25.9)</td>
<td>0.26 (0.11, 0.40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
<td>0.39 (25.8)</td>
<td>0.21 (0.06, 0.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
<td>0.18 (10.2)</td>
<td>0.21 (0.13, 0.29)</td>
<td></td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
<td>0.43 (29.0)</td>
<td>0.21 (0.13, 0.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>277</td>
<td>0.47 (32.5)</td>
<td>0.24 (0.16, 0.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
<td>0.22 (14.4)</td>
<td>0.21 (0.13, 0.29)</td>
<td></td>
</tr>
</tbody>
</table>

**At the time of the database lock, not all patients had completed Week 52**

**Figure 3: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Baseline Blood Eosinophils ≥ 300 cells/mcL (AS Trial 2)**

**Figure 4: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV<sub>1</sub> across Baseline Blood Eosinophil Counts (cells/mL) in AS Trial 2**

**Additional Secondary Endpoints**

ACQ-5 and AQLQ(S) were assessed in AS Trial 2 at 52 weeks. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)).

- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in the overall population was 69% vs 62% placebo (odds ratio 1.37; 95% CI: 1.01, 1.86) and 69% vs 63% placebo (odds ratio 1.28; 95% CI: 0.94, 1.73), respectively, and the AQLQ(S) responder rates were 62% vs 54% placebo (odds ratio 1.61; 95% CI: 1.17, 2.21) and 62% vs 57% placebo (odds ratio 1.33; 95% CI: 0.98, 1.81), respectively.

- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in subjects with baseline blood eosinophil counts ≥ 300 cells/mL was 75% vs 67% placebo (odds ratio: 1.46; 95% CI: 1.09, 2.04), and 71% vs 64% placebo (odds ratio: 1.39; 95% CI: 0.88, 2.19), respectively; and the AQLQ(S) responder rates were 71% vs 55% placebo (odds ratio 2.02; 95% CI: 1.24, 3.32) and 65% vs 55% placebo (odds ratio 1.79; 95% CI: 1.13, 2.65), respectively.

**Oral Corticosteroid Reduction**

AS Trial 3 evaluated the effect of DUPIXENT on reducing the use of maintenance oral corticosteroids. The baseline mean oral corticosteroid dose was 12 mg in the placebo group and 11 mg in the group receiving DUPIXENT. The primary endpoint was the percent reduction from baseline of the final oral corticosteroid dose at Week 24 while maintaining asthma control. Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT (95% CI: 60%, 80%) compared to 42% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 92 (80%) subjects receiving DUPIXENT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Week 24 was 72% for DUPIXENT and 37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPIXENT versus 31 (29%) subjects in the placebo group had a 100% reduction in their OCS dose.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were lower in subjects receiving DUPIXENT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPIXENT and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV<sub>1</sub> from baseline to Week 24 was greater in subjects receiving DUPIXENT compared with those receiving placebo (LS mean difference for DUPIXENT versus placebo of 0.22 L [95% CI: 0.09, 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in AS Trial 3 and showed improvements similar to those in AS Trial 2.

**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 either 300 mg of DUPIXENT in 2 mL (NDC 0024-5914-00) or 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00).

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

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>300 mg/2 mL Pre-filled Syringe with Needle Shield</th>
<th>200 mg/1.14 mL Pre-filled Syringe with Needle Shield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 2 syringes</td>
<td>NDC 0024-5914-01</td>
<td>NDC 0024-5918-01</td>
</tr>
</tbody>
</table>

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.

Do NOT freeze. 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)].

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis [see Warnings and Precautions (5.3)].

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT [see Warnings and Precautions (5.4)].

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see Warnings and Precautions (5.5)].

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see Warnings and Precautions (5.6)].

Manufactured by:
Regeneron Pharmaceuticals, Inc.
Tarrytown, NY 10591
U.S. License No. 1760

Marketed by:
sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

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