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

**INDICATIONS AND USAGE**

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- for the treatment of patients aged 6 years and older 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)
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). (1.3)

**Limitation of Use**

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

**DOSAGE AND ADMINISTRATION**

Administer by subcutaneous injection. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older. (1.2)

**Atopic Dermatitis**

**Adults**

- 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 (Q2W). (2.1)

**Pediatric Patients**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Dose</th>
<th>Subsequent Doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg Q4W</td>
</tr>
<tr>
<td>30 to less than 60 kg</td>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg Q2W</td>
</tr>
<tr>
<td>60 kg or more</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg Q2W</td>
</tr>
</tbody>
</table>

* Q2W – every other week; Q4W – every 4 weeks

**Asthma**

- The recommended dose of DUPIXENT 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

**Full Prescribing Information: Contents**

1 INDICATIONS AND USAGE
   1.1 Atopic Dermatitis
   1.2 Asthma
   1.3 Chronic Rhinosinusitis with Nasal Polyps

2 DOSAGE AND ADMINISTRATION
   2.1 Atopic Dermatitis
   2.2 Asthma
   2.3 Chronic Rhinosinusitis with Nasal Polyps
   2.4 Important Administration Instructions
   2.5 Preparation for Use of DUPIXENT

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
   5.1 Hypersensitivity
   5.2 Conjunctivitis and Keratitis
   5.3 Eosinophilic Conditions
   5.4 Acute Asthma Symptoms or Deteriorating Disease
   5.5 Reduction of Corticosteroid Dosage
   5.6 Patients with Co-morbid Asthma

6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Immunogenicity
   6.3 Postmarketing Experience

7 DRUG INTERACTIONS
   7.1 Live Vaccines
   7.2 Non-Live Vaccines

8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation
   8.4 Pediatric Use
   8.5 Geriatric Use

9 OVERDOSE

10 DESCRIPTION

11 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics

5.7 Parasitic (Helminth) Infections

6 ADVERSE REACTIONS

12 CLINICAL PHARMACOLOGY

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

Revised: 06/2021
Concomitant Topical Therapies

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.

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.

1.3 Chronic Rhinosinusitis with Nasal Polyps

DUPIXENT is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection, either by pre-filled syringe or pre-filled pen. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older.

2.1 Atopic Dermatitis

Dosing in Adults

The recommended dose of DUPLEXEN for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosing in Pediatric Patients (6 to 17 Years of Age)

The recommended dose of DUPLEXENT for patients 6 to 17 years of age is specified in Table 1.

Table 1: Dose of DUPLEXENT for Subcutaneous Administration in Pediatric Patients (6 to 17 Years of Age)

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Dose</th>
<th>Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every 4 weeks (Q4W)</td>
</tr>
<tr>
<td>30 to less than 60 kg</td>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every other week (Q2W)</td>
</tr>
<tr>
<td>60 kg or more</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every other week (Q2W)</td>
</tr>
</tbody>
</table>

Concomitant Topical Therapies

DUPLEXENT 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 co-morbid 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 Chronic Rhinosinusitis with Nasal Polyps

The recommended dose of DUPLEXENT for adult patients is 300 mg given every other week.

2.4 Important Administration Instructions

DUPLEXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPLEXENT after training in subcutaneous injection technique using the pre-filled syringe or pre-filled pen. The DUPLEXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older. In adolescents 12 years of age and older, it is recommended that DUPLEXENT be given by or under the supervision of an adult.

DUPLEXENT pre-filled syringe should be given by a caregiver in children 6-11 years of age. Provide proper training to patients and/or caregivers on the preparation and administration of DUPLEXENT prior to use according to the “Instructions for Use”.

For atopic dermatitis and asthma patients taking an initial 600 mg dose, administer each of the two DUPLEXENT 300 mg injections at different injection sites.

For atopic dermatitis and asthma patients taking an initial 400 mg dose, administer each of the two DUPLEXENT 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 DUPLEXENT into skin that is tender, damaged, bruised, or scarred.

If an every other week 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.

If an every 4 week 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 administer the dose, starting a new schedule based on this date.

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

2.5 Preparation for Use of DUPLEXENT

Before injection, remove DUPLEXENT from the refrigerator and allow DUPLEXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen and 30 minutes for the 200 mg/1.14 mL pre-filled syringe or pre-filled pen) 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 or pre-filled pen.

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
- Injection: 300 mg/2 mL in a single-dose pre-filled pen
- Injection: 200 mg/1.14 mL in a single-dose pre-filled pen

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 or keratitis recovered or were recovering during the treatment period [see Adverse Reactions (6.1)]. Among asthma subjects, the frequencies of conjunctivitis and keratitis were similar between DUPLEXENT and placebo [see Adverse Reactions (6.1)].

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPLEXENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [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 reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash,
worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations.

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

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. 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 Patients with Co-Morbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have co-morbid 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 DUPIXENT will influence the immune response against helminth infections.

Advise 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 treatment, discontinue treatment with DUPIXENT 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 observed in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were White, 24% were Asian, and 6% were Black; in terms of co-morbid conditions, 48% of the subjects had asthma, 43% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

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

Weeks 0 to 16 (Trials 1 to 4)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W monotherapy and placebo groups. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 2: 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 Monotherapya</th>
<th>DUPIXENT + TCSb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=529 n (%)</td>
<td>N=517 n (%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo + TCS</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>51 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td></td>
<td>11 (10)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Conjunctivitisc</td>
<td>51 (10)</td>
<td>12 (2)</td>
</tr>
<tr>
<td></td>
<td>10 (9)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>5 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td></td>
<td>3 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16 (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapya</th>
<th>DUPIXENT + TCSb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=517 n (%)</td>
<td>N=110 n (%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo + TCS</td>
</tr>
<tr>
<td>Other herpes simplex virus infectiond</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td></td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2 (2)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16 (continued)

a Pooled analysis of Trials 1, 2, and 4.

b Analysis of Trial 3 where subjects were on background TCS therapy.

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

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

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

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

Safety through Week 52 (Trial 3)

In 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 the DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

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

Adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Children with Atopic Dermatitis (6 to 11 Years of Age)

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 367 subjects 6 to 11 years of age with severe atopic dermatitis (Trial 8). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and adolescents with atopic dermatitis.

The long-term safety of DUPIXENT + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (Trial 7). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe atopic dermatitis at the time of enrollment in Trial 7. The safety profile of DUPIXENT + TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in pediatric subjects was consistent with that seen in adults and adolescents with atopic dermatitis [see Use in Specific Populations (8.4)].

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 2110 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were White. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.
Table 3: Adverse Reactions Occurring in ≥1% of the DUXIPENT 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>DUXIPENT 200 mg Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=779 (n %)</td>
<td>N=788 (n %)</td>
<td>N=792 (n %)</td>
</tr>
<tr>
<td>Injection site reactionsa</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophiliab</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

a Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.
b Eosinophilia = blood eosinophils ≥3,000 cells/mL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions [see Warnings and Precautions (5.3)].

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

Table 4: Adverse Reactions Occurring in ≥1% of the DUXIPENT Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N=440 (n %)</th>
<th>N=282 (n %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactionsa</td>
<td>28 (6%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (1%)</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

a Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.
b Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

The safety profile of DUXIPENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Conjunctivitis and Keratitis

During the 52-week treatment period of concomitant therapy with topical corticosteroids (TCS) atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUXIPENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). In DUXIPENT atopic dermatitis monotherapy trials (Trials 1, 2, and 4) through Week 16, keratitis was reported in <1% of the DUXIPENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis DUXIPENT + topical corticosteroids (TCS) atopic dermatitis trial (Trial 3), keratitis was reported in 4% of the DUXIPENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among asthma subjects, the frequency of conjunctivitis was similar between DUXIPENT and placebo. In the 52-week CRSwNP study (CSNP Trial 2), the frequency of conjunctivitis was 3% in the DUXIPENT subjects and 1% in the placebo subjects; all of these subjects recovered [see Warnings and Precautions (5.2)].

Eczea Herpetica and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUXIPENT groups in the atopic dermatitis trials.

Hypersensitivity Reactions

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

Eosinophils

DUXIPENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUXIPENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUXIPENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined toward baseline levels during study treatment [see Warnings and Precautions (5.3)].

Cardiovascular

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 (0.2%) of the DUXIPENT 200 mg Q2W group, 4 (0.5%) of the DUXIPENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUXIPENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUXIPENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

In the 24-week placebo controlled trial in subjects with CRSwNP (CSNP Trial 1), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the DUXIPENT group and 0 (0.0%) of the placebo group. In the 1-year placebo controlled trial in subjects with CRSwNP (CSNP Trial 2), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUXIPENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies. Similar results were observed in pediatric subjects (8 to 11 years of age) with atopic dermatitis who received DUXIPENT 200 mg Q2W or 300 mg Q4W for 16 weeks. Approximately 16% of adolescent subjects with atopic dermatitis who received DUXIPENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

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

Regardless of age or population, approximately 2% to 4% of subjects in placebo groups were positive for antibodies to DUXIPENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUXIPENT and placebo subjects were mostly low. In subjects who received DUXIPENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations [see Clinical Pharmacology (12.3)].

Two adult subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUXIPENT therapy [see Warnings and Precautions (5.3)].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of DUXIPENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Facial Rash

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUXIPENT.

7.2 Non-Live Vaccines

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUXIPXNT during pregnancy. Healthcare providers and patients may call 1-877-311-8972 or go to https://motherstopbaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUXIPXNT 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, DUXIPXNT 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 10-10 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. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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 preeclampsia in the mother and/or prematurity, 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 cynomolgous monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 100 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 DUXIPXNT and any potential adverse effects on the breastfed child from DUXIPXNT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUXIPXNT have been established in pediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis.

Use of DUXIPXNT in this age group is supported by Trial 6 which included 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis and Trial 8 which included 367 children ages 6 to 11 years old with severe atopic dermatitis. The safety and efficacy were generally consistent between pediatric and adult patients (see Adverse Reactions (6.1) and Clinical Studies (14.1)).

Use is also supported by Trial 7, an open-label extension study that enrolled subjects who were vaccinated with the Tdap vaccine (Adacel) and a meningococcal polysaccharide vaccine (Menomune), Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

A total of 107 adolescents aged 12 to 17 years of age and older with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUXIPXNT (or matching placebo, either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For 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 adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than in adults at the respective dose level which was mainly accounted for by lower body weight (see Clinical Pharmacology (12.3)).

The adverse event profile in adolescents was generally similar to the adults (see Adverse Reactions (6.1)).

CRSwNP

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<18 years of age) with CRSwNP have not been established.

8.5 Geriatric Use

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

Of the 1977 subjects with asthma exposed to DUXIPXNT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

Of the 440 subjects with CRSwNP exposed to DUXIPXNT, a total of 79 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUXIPXNT overdose. In the event of overdose, 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.

DUXIPXNT (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUXIPXNT is provided as either a single-dose pre-filled syringe with needle shield or a single dose pre-filled pen in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe or pre-filled pen 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 or pre-filled pen delivers 200 mg dupilumab in 1.14 mL which also contains L-arginine hydrochloride (12 mg), L-histidine (5.3 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, atopic dermatitis, and CRSwNP. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines, chemokines) are involved in inflammation. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE; however, the mechanism of dupilumab action in asthma has not been definitively established.

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and peristin were decreased relative to placebo. These reductions in biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal after 2 weeks of treatment, except for IgE which decreased more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (AS Trial 1) and 70% at Week 52 (AS Trial 2). For FeNO, the mean percent reduction from baseline at Week 52 was 33% and 24% in AS Trials 1 and 2 respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with atopic dermatitis, asthma, and CRSwNP.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations (Cmax) of 70.1±24.1 mcg/mL, 41.8±12.4 mcg/mL, or 30.5±9.39 mcg/mL respectively, by approximately 1 week post dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose every 2 weeks (twice the recommended dosing frequency) or Q2W dose, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.
The bioavailability of dupilumab following a SC dose is similar between AD, asthma, and CRSwNP patients, ranging between 61% and 64%.

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

### Elimination
The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W, 300 mg QW, or 200 mg Q2W dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10-12, 13, and 9 weeks, respectively.

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

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

### Age
Based on population pharmacokinetic analysis, age did not affect dupilumab clearance.

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

#### Specific Populations

##### Geriatric Patients
In subjects who are 65 years and older, the mean ± SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered Q2W and weekly, and 30.7±11.7 mcg/mL for 200 mg administered Q2W.

##### Pediatric Patients
For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with 200 mg (~60 kg) or 300 mg (~80 kg), the mean ± SD steady-state trough concentration of dupilumab was 94.5±27.0 mcg/mL, respectively.

For children 6 to 11 years of age with atopic dermatitis receiving every other week dosing (Q2W) with 200 mg (~30 kg) or every four week dosing (Q4W) with 300 mg (~30 kg), the mean ± SD steady-state trough concentration was 86.0±34.6 mcg/mL and 98.7±33.2 mcg/mL, respectively.

##### Asthma
A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in AS Trial 2. The mean ± SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered Q2W.

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

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

#### Cytochrome P450 Substrates
The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were non-detectable concentration (<78 ng/mL) are 10-12, 13, and 9 weeks, respectively.

### NONCLINICAL TOXICOLOGY

#### 13 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab.

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

### CLINICAL STUDIES

#### 14.1 Atopic Dermatitis
Adults with Atopic Dermatitis
Three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3: NCT02277714, 02277769, and 02260986 respectively) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator’s Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, and Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were White, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

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

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

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

Clinical Response at Week 16 (Trials 1, 2, and 3)
The results of the DUPLEX monotherapy trials (Trials 1 and 2) and the DUPLEX with concomitant TCS trial (Trial 3) are presented in Table 5.

### Table 5: Efficacy Results of DUPLEX With or Without Concomitant TCS at Week 16 (FAS)

<table>
<thead>
<tr>
<th>Trial</th>
<th>DUPLEX 300 mg Q2W</th>
<th>Placebo</th>
<th>DUPLEX 300 mg Q2W</th>
<th>Placebo</th>
<th>DUPLEX 300 mg Q2W + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects randomized (FAS)</td>
<td>224</td>
<td>224</td>
<td>233</td>
<td>236</td>
<td>106</td>
<td>315</td>
</tr>
<tr>
<td>IGA 0 or 1</td>
<td>38%</td>
<td>10%</td>
<td>36%</td>
<td>9%</td>
<td>39%</td>
<td>12%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>51%</td>
<td>15%</td>
<td>44%</td>
<td>12%</td>
<td>69%</td>
<td>23%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>36%</td>
<td>8%</td>
<td>30%</td>
<td>7%</td>
<td>40%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* Full Analysis Set (FAS) includes all subjects randomized.

### Figure 1: Proportion of Subjects with ≥4-point Improvement on the Peak Pruritus NRS in Trial 1 and Trial 2 Studies (FAS)

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 DUPLEX 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 DUPLEX IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPLEX with concomitant TCS trial (Trial 3) are presented in Table 6.
The efficacy results at Week 16 for Trial 6 are presented in Table 7.

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: 55 (53%) in the Q2W group and 3 (10%) in the placebo group.

Adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The efficacy and safety of DUPIXENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03054428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥20%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

Subjects in the DUPIXENT group with baseline weight <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight ≥60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In Trial 6, the mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline, 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had prior systemic immunosuppressants. Also, at baseline, the mean EASI score was 36, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 61% had food allergies, and 60% had allergic rhinitis, 47% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 for Trial 6 are presented in Table 7.

### Table 6: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52

<table>
<thead>
<tr>
<th></th>
<th>DUPIXENT 300 mg Q2W + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>89</td>
<td>264</td>
</tr>
<tr>
<td>Responder&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Responder at Week 16</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Non-responder at Week 16</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-responder at Week 52</td>
<td>44%</td>
<td>80%</td>
</tr>
<tr>
<td>Overall Responder&lt;sup&gt;b&lt;/sup&gt; Rate at Week 52</td>
<td>36%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> Responder was defined as a subject with an IGA 0 or 1 (“clear” or “almost clear”) and a reduction of ≥2 points on a 0-4 IGA scale.

<sup>c</sup> Subjects who received rescue treatment or with missing data were considered as non-responders.

### Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)<sup>d</sup>

<table>
<thead>
<tr>
<th></th>
<th>DUPIXENT&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Placebo N=85&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA 0 or 1</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>37%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Full Analysis Set (FAS) includes all subjects randomized.

<sup>b</sup> Responder was defined as a subject with an IGA 0 or 1 (“clear” or “almost clear”) and a reduction of ≥2 points on a 0-4 IGA scale.

<sup>c</sup> Subjects who received rescue treatment or with missing data were considered as non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively).

<sup>d</sup> At Week 0, subjects received 400 mg (baseline weight <60 kg) or 600 mg (baseline weight ≥60 kg) of DUPIXENT.

A greater proportion of subjects randomized to DUPIXENT achieved an improvement in the Peak Pruritus NRS compared to placebo (defined as ≥4-point improvement at Week 4). See Figure 2.
The demographics and baseline characteristics of these 3 trials are provided in Table 9 below.

<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 FEV₁ (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 FEV₁ 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 (A0 %, NP %, AR %)</td>
<td>73 (8, 11, 62)</td>
<td>76 (8, 10, 13, 69)</td>
<td>72 (8, 21, 56)</td>
</tr>
<tr>
<td>Mean FeNO ppb (± SD)</td>
<td>38 (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>
<tr>
<td>Mean baseline blood eosinophil count (± SD) cells/mL</td>
<td>350 (430)</td>
<td>360 (370)</td>
<td>350 (310)</td>
</tr>
</tbody>
</table>

**CS** = inhaled corticosteroid; **FEV₁** = Forced expiratory volume in 1 second; **AD** = atopic dermatitis; **NP** = nasal polyposis; **AR** = allergic rhinitis; **FeNO** = fraction of exhaled nitric oxide

**Exacerbations**

As Trials 1 and 2 and 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 ≥300 cells/mL) in AS Trial 1 and the overall population in AS Trial 2, subjects receiving either DUPIXENT 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 DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.87. 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 DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mL in AS Trial 1 and 2 are shown in Table 10.

Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 4. Pre-specified subgroup analyses of 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 DUPIXENT and placebo.

In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUPIXENT 200 mg or 300 mg Q2W, respectively.

<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>Rate (95% CI)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
<td>0.30 (0.13, 0.68)</td>
<td>0.29 (0.11, 0.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
<td>0.20 (0.08, 0.52)</td>
<td>0.19 (0.07, 0.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
<td>1.04 (0.57, 1.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
<td>0.37 (0.29, 0.48)</td>
<td>0.34 (0.24, 0.48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
<td>1.08 (0.85, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
<td>0.40 (0.32, 0.51)</td>
<td>0.33 (0.23, 0.45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
<td>1.24 (0.97, 1.57)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in AS Trial 2 (Figure 5).

Significant increases in pre-bronchodilator FEV₁ 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 FEV₁ 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 11. Improvements in FEV₁ by baseline blood eosinophils for AS Trial 2 are shown in Figure 6. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Table 11: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV₁, 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>LS Mean Change from baseline (%)</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>0.43 (25.9)</td>
<td>0.26</td>
<td>(0.11, 0.40)</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>0.39 (25.8)</td>
<td>0.21</td>
<td>(0.06, 0.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.18 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>0.43 (29.0)</td>
<td>0.21</td>
<td>(0.13, 0.29)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.21 (15.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>0.47 (32.5)</td>
<td>0.24</td>
<td>(0.16, 0.32)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.22 (14.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in subjects receiving DUPIXENT (95% CI: 69%, 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 82 (80%) subjects receiving DUPIXENT compared to 57 (63%) 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 4.45 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 corticosteroids) were observed at Week 12 for AS Trials 1 and 2 in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS).
prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator’s discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg DUPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg DUPIXENT (N=150) every other week for 52 weeks, 300 mg DUPIXENT (N=145) every other week until week 24 followed by 300 mg DUPIXENT every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries. 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers, and change from baseline to Week 24 in nasal congestion obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the inferior border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sino-nasal outcome test (SNOT-22). The LMK sinus CT scan score evaluated the opacification of each sinus using a 0 to 3 scale (0=no opacification; 1=partial opacification; 2=total opacification) deriving a maximum score of 12 per side and a total maximum score of 24 (higher scores indicate more opacification). Loss of smell was scored reflectively by the patient every morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22 had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to Week 52) were evaluated.

The demographics and baseline characteristics of these 2 trials are provided in Table 12 below.

Table 12: Demographics and Baseline Characteristics of CRSwNP Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSNP Trial 1 (N=276)</th>
<th>CSNP Trial 2 (N=448)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>50 (13)</td>
<td>52 (12)</td>
</tr>
<tr>
<td>% Male</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>Mean CRSwNP duration (years) (SD)</td>
<td>11 (9)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Patients with ≥ 1 prior surgery (%)</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Patients with systemic corticosteroid use in the previous 2 years (%)</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Mean Bilateral endoscopic NPS* (SD), range 0-8</td>
<td>5.8 (1.3)</td>
<td>6.1 (1.2)</td>
</tr>
<tr>
<td>Mean Nasal congestion (NC) score* (SD), range 0-3</td>
<td>2.4 (0.6)</td>
<td>2.4 (0.6)</td>
</tr>
<tr>
<td>Mean LMK sinus CT total score* (SD), range 0-24</td>
<td>19 (4.4)</td>
<td>18 (3.8)</td>
</tr>
<tr>
<td>Mean loss of smell score* (AM), (SD), range 0-3</td>
<td>2.7 (0.5)</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>Mean SNOT-22 total score* (SD), range 0-110</td>
<td>49.4 (20.2)</td>
<td>51.9 (20.9)</td>
</tr>
<tr>
<td>Mean blood eosinophils (cells/μL) (SD)</td>
<td>440 (330)</td>
<td>430 (350)</td>
</tr>
<tr>
<td>Mean total IgE IU/mL (SD)</td>
<td>212 (276)</td>
<td>240 (342)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>NSAID-ERD (%)</td>
<td>30</td>
<td>27</td>
</tr>
</tbody>
</table>

* Higher scores indicate greater disease severity
SD = standard deviation; AM = morning; NPS = nasal polyps score; SNOT-22 = 22-item sino-nasal outcome test; NSAID-ERD = asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (CSNP Trial 1 and CSNP Trial 2)
The results for primary endpoints in CRSwNP studies are presented in Table 13.

Table 13: Results of the Primary Endpoints in CRSwNP Trials

<table>
<thead>
<tr>
<th>CSNP Trial 1</th>
<th>CSNP Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=133)</td>
<td>DUPLEXENT 300 mg Q2W (n=143)</td>
</tr>
<tr>
<td>Base Line mean</td>
<td>LS mean change</td>
</tr>
<tr>
<td>NPS</td>
<td>5.86</td>
</tr>
<tr>
<td>NC</td>
<td>2.45</td>
</tr>
</tbody>
</table>

A reduction in score indicates improvement.
NPS = nasal polyps score; NC = nasal congestion obstruction

Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 8).

Figure 8: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in CSNP Trial 2 - ITT Population
In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV₁ surgery and without prior surgery. The effects of DUPIXENT on the primary endpoints of NPS and nasal congestion and the CSNP Trial 2 Pooled Figure 10: Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46). The proportion of subjects who was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The total number of systemic corticosteroid courses per year was reduced by 83% (95% CI: 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (95% CI: 0.25, 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17, 95% CI: 0.07, 0.46).

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with DUPIXENT resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 10). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17, 95% CI: 0.07, 0.46).

Dulimumab significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.10 (95% CI: -1.31, -0.89). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4.

The effects of DUPIXENT on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in patients with prior surgery and without prior surgery. In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV₁, were similar to patients in the asthma program.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dulimumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield or pre-filled pens. 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 0024-5915-00). Each pre-filled pen is designed to deliver either 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00) or 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5919-00). DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield or 2 pre-filled pens.

<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>

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>300 mg/2 mL Pre-filled Pen</th>
<th>200 mg/1.14 mL Pre-filled Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 2 pens</td>
<td>NDC 0024-5915-02</td>
<td>NDC 0024-5919-02</td>
</tr>
</tbody>
</table>

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, DUPIXENT 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 DUPIXENT to heat or direct sunlight. Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation and advise patients about how they may enroll in the registry [see Use in Specific Populations (8.1)].

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)].

Patients with Co-morbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have co-morbid 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)

DUPIXENT™ is a registered trademark of Sanofi Biotechnology

© 2021 Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC. All rights reserved.
What is DUPIXENT?
DUPIXENT is a prescription medicine used:
- to treat people aged 6 years and older with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids.
- with other asthma medicines for the maintenance treatment of moderate-to-severe asthma in people aged 12 years and older whose asthma is not controlled with their current asthma medicines. DUPIXENT helps prevent severe asthma attacks (exacerbations) and can improve your breathing. DUPIXENT may also help reduce the amount of oral corticosteroids you need while preventing severe asthma attacks and improving your breathing.
- with other medicines for the maintenance treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled.

- DUPIXENT is not used to treat sudden breathing problems.
- DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.
- It is not known if DUPIXENT is safe and effective in children with atopic dermatitis under 6 years of age.
- It is not known if DUPIXENT is safe and effective in children with asthma under 12 years of age.
- It is not known if DUPIXENT is safe and effective in children with chronic rhinosinusitis with nasal polyposis under 18 years of age.

Do not use DUPIXENT if you are allergic to dupilumab or to any of the ingredients in DUPIXENT. See the end of this leaflet for a complete list of ingredients in DUPIXENT.

Before using DUPIXENT, tell your healthcare provider about all your medical conditions, including if you:
- have eye problems
- have a parasitic (helminth) infection
- are scheduled to receive any vaccinations. You should not receive a “live vaccine” if you are treated with DUPIXENT.
- are pregnant or plan to become pregnant. It is not known whether DUPIXENT will harm your unborn baby.

Pregnancy Exposure Registry. There is a pregnancy exposure registry for women who take DUPIXENT during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Your healthcare provider can enroll you in this registry. You may also enroll yourself or get more information about the registry by calling 1-877-311-8972 or going to https://mothertobaby.org/ongoing-study/dupixent/.
- are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you:
- are taking oral, topical, or inhaled corticosteroid medicines
- have asthma and use an asthma medicine
- have atopic dermatitis or CRSwNP, and also have asthma

Do not change or stop your corticosteroid medicine or other asthma medicine without talking to your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine or other asthma medicine to come back.

How should I use DUPIXENT?
- See the detailed “Instructions for Use” that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes and pre-filled pens.
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- Your healthcare provider will tell you how much DUPIXENT to inject and how often to inject it.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield or as a pre-filled pen.
- DUPIXENT is given as an injection under the skin (subcutaneous injection).
- If your healthcare provider decides that you or a caregiver can give the injections of DUPIXENT, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. Do not try to inject DUPIXENT until you have been shown the right way by your healthcare provider. In children 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. In children younger than 12 years of age, DUPIXENT should be given by a caregiver.
- If your dose schedule is every other week and you miss a dose of DUPIXENT: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- If your dose schedule is every 4 weeks and you miss a dose of DUPIXENT: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, start a new every 4 week dose schedule from the time you remember to take your DUPIXENT injection.

If you inject more DUPIXENT than prescribed, call your healthcare provider right away.
- Your healthcare provider may prescribe other medicines to use with DUPIXENT. Use the other prescribed medicines exactly as your healthcare provider tells you to.

What are the possible side effects of DUPIXENT?
DUPIXENT can cause serious side effects, including:
- Allergic reactions (hypersensitivity), including a severe reaction known as anaphylaxis. Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following symptoms:
  - breathing problems
  - fever
  - general ill feeling
  - swollen lymph nodes
  - swelling of the face, mouth, and tongue
  - hives
  - itching
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - joint pain
  - skin rash

Instructions for Use

• **Eye problems.** Tell your healthcare provider if you have any new or worsening eye problems, including eye pain or changes in vision.

• **Inflammation of your blood vessels.** Rarely, this can happen in people with asthma who receive DUPIXENT. This may happen in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. It is not known whether this is caused by DUPIXENT. Tell your healthcare provider right away if you have:
  
  o rash  
  o shortness of breath  
  o chest pain  
  o a feeling of pins and needles or numbness of your arms or legs  
  o persistent fever

The most common side effects of DUPIXENT include:

• injection site reactions  
• eye and eyelid inflammation, including redness, swelling, and itching  
• pain in the throat (oropharyngeal pain)  
• cold sores in your mouth or on your lips  
• high count of a certain white blood cell (eosinophilia)  
• trouble sleeping (insomnia)  
• toothache  
• gastritis  
• joint pain (arthralgia)

The following additional side effects have been reported with DUPIXENT:

• facial rash or redness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of DUPIXENT.

Tell your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

---

**General information about the safe and effective use of DUPIXENT.**
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DUPIXENT for a condition for which it was not prescribed. Do not give DUPIXENT to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DUPIXENT that is written for health professionals.

---

**What are the ingredients in DUPIXENT?**
Active ingredient: dupilumab
Inactive ingredients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, and water for injection.

**REGENERON | SANOFI GENZYME**
Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License No. 1760
Marketed by: sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

DUPIXENT® is a registered trademark of Sanofi Biotechnology / © 2021 Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC. All rights reserved.

For more information about DUPIXENT, go to www.DUPIXENT.com or call 1-844-DUPIXENT (1-844-387-4936).

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: January 2021

DUP.21.06.0040