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 of patients aged 6 years and older with moderate-to-severe asthma characterized by 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)

Limitations of Use

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

DOSE 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

Dosage in Adults

The recommended dosage 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)

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


<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading Dose</th>
<th>Subsequent Dose</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

Dosage in Adults and Adolescents (12 Years and Older)


<table>
<thead>
<tr>
<th>Initial Loading Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every 2 weeks (Q2W)</td>
</tr>
</tbody>
</table>
| or
| 600 mg (two 300 mg injections) | 300 mg every 2 weeks (Q2W) |

Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis

600 mg (two 300 mg injections) 300 mg every 2 weeks (Q2W)

For pediatric patients (6 to 11 years old) with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 1 which includes an initial loading dose. (2.1)

Chronic Rhinosinusitis with Nasal Polyposis

• The recommended dosage of DUPIXENT for adult patients is 300 mg given every other week. (2.3)

DOSE FORMS AND STRENGTHS

Injection: 100 mg/0.67 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)

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

Injection: 300 mg/2 mL solution in a single-dose pre-filled pen. (3)

Injection: 100 mg/0.67 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, erythema multiforme, anaphylaxis, and serum sickness) have occurred after administration of DUPIXENT. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)

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

• Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, 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 treatment, discontinue treatment with DUPIXENT until the infection resolves. (5.7)

ADVERSE REACTIONS

Atopic Dermatitis: Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes viruses, oropharyngeal pain, and eosinophilia. (6.1)

Asthma: Most common adverse reactions (incidence ≥1%) are injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)

Chronic Rhinosinusitis with Nasal Polyposis: Most common adverse reactions (incidence ≥1%) are injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)

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

DRUG INTERACTIONS

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

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

Revised: 10/2021
Dosage in Adults
oral corticosteroid dependent asthma

2.1 Atopic Dermatitis

DUPIXENT is indicated as an add-on maintenance 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.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment of patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma [see Clinical Studies (14)].

Limitations of Use

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

1.3 Chronic Rhinosinusitis with Nasal Polypsis

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

Dosage in Adults

The recommended dosage of DUPIXENT for adult patients is 300 mg given every other week (Q2W).

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

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

Table 1: Dosage of DUPIXENT for Subcutaneous Administration in Pediatric Patients (6 to 17 Years of Age) with Atopic Dermatitis

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading 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

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

Dosage in Adults and Adolescents (12 Years and Older)

The recommended dosage of DUPIXENT for adults and adolescents (12 years of age and older) is specified in Table 2.

Table 2: Dosage of DUPIXENT for Subcutaneous Administration in Adults and Adolescents 12 Years and Older with Asthma

<table>
<thead>
<tr>
<th>Initial Loading Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every 2 weeks (Q2W)</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every 2 weeks (Q2W)</td>
</tr>
</tbody>
</table>

Dosage in Pediatric Patients (6 to 11 Years of Age)

The recommended dosage of DUPIXENT for patients 6 to 11 years of age is specified in Table 3.

Table 3: Dosage of DUPIXENT for Subcutaneous Administration in Pediatric Patients 6 to 11 Years of Age with Asthma

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial* and Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>200 mg every other week (Q2W)</td>
</tr>
</tbody>
</table>

* For pediatric patients (6 to 11 years old) with asthma, no initial loading dose is recommended.

For pediatric patients (6 to 11 years old) with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 1 which includes an initial loading dose [see Dosage and Administration (2.1)].

2.3 Chronic Rhinosinusitis with Nasal Polyposis

The recommended dosage of DUPIXENT for adult patients is 300 mg given every other week by subcutaneous injection.

2.4 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 or pre-filled pen. The DUPIXENT 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 DUPIXENT be given by or under the supervision of an adult. DUPIXENT pre-filled syringe should be administered by a caregiver in pediatric patients 6 to 11 years of age. 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 atopic dermatitis and asthma patients taking an initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

For atopic dermatitis and asthma patients taking an 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.

Missed Dose Information

If an every other week dose is missed, 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 DUXIPENT “Instructions for Use” contains more detailed instructions on the preparation and administration of DUXIPENT [see Instructions for Use].

2.5 Preparation for Use of DUXIPENT

Before injection, remove DUXIPENT from the refrigerator and allow DUXIPENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen, 30 minutes for the 200 mg/1.14 mL pre-filled syringe or pre-filled pen, and 200 mg/0.67 mL pre-filled syringe) without removing the needle cap.

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

3 DOSAGE FORMS AND STRENGTHS

DUXIPENT is a clear to slightly opalescent, colorless to pale yellow solution available as:
- Injection: 300 mg/2 mL in a single-dose pre-filled pen
- 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 pen
- Injection: 200 mg/1.14 mL in a single-dose pre-filled syringe with needle shield
- Injection: 100 mg/0.67 mL in a single-dose pre-filled syringe with needle shield

4 CONTRAINDICATIONS

DUXIPENT 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, erythema multiforme, and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUXIPENT 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 DUXIPENT [see Adverse Reactions (6.1, 6.2)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUXIPENT. 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 DUXIPENT and placebo [see Adverse Reactions (6.1)].

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUXIPENT 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 consisting of churg-strauss vasculitis or polyarteritis nodosa have been reported with DUXIPENT 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 DUXIPENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Risk Associated with Abrupt Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUXIPENT. 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 DUXIPENT will influence the immune response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with DUXIPENT. If patients become infected while receiving treatment with DUXIPENT and do not respond to anti-helminth treatment, discontinue treatment with DUXIPENT until the infection resolves. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric patients 6 to 11 years old who participated in the pediatric asthma development program [see Adverse Reactions (6.1)].

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.

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 DUXIPENT 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, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUXIPENT, with or without concomitant topical corticosteroids (TCS). A total of 739 subjects were treated with DUXIPENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

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

Trial 9 is a multicenter, open-label extension (OLE) study which assessed the long-term safety of repeat doses of DUXIPENT (through 148 weeks of treatment) in adults with moderate-to-severe AD who had previously participated in controlled studies of atopic dermatitis or had been screened for Trial 1 or Trial 2. The safety data in Trial 9 reflect exposure to DUXIPENT in 2677 subjects, including 2254 exposed for at least 52 weeks, 1192 exposed for at least 100 weeks, and 357 exposed for at least 148 weeks. In Trial 9, 9.7% of subjects were exposed to DUXIPENT 300 mg weekly dosing (QW).

Weeks 0 to 16 (Trials 1 to 4)

In DUXIPENT 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 DUXIPENT 300 mg Q2W and placebo groups. Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUXIPENT 300 mg Q2W monotherapy groups, and in the DUXIPENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 4: Adverse Reactions Occurring in ≥1% of the DUXIPENT Monotherapy Group or the DUXIPENT + TCS Group in the Atopic Dermatitis Trials through Week 16

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUXIPENT Monotherapy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo</th>
<th>DUXIPENT Monotherapy&lt;sup&gt;b&lt;/sup&gt; + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury site reaction</td>
<td>51 (10)</td>
<td>28 (5)</td>
<td>11 (10)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Conjunctivitis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51 (10)</td>
<td>12 (2)</td>
<td>10 (9)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>5 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Oral herpetic</td>
<td>20 (4)</td>
<td>8 (2)</td>
<td>3 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Keratitis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Eye prunus</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10 (2)</td>
<td>6 (1)</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (2)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pooled analysis of Trials 1, 2, and 4.
<sup>b</sup> Analysis of Trial 3 where subjects were on background TCS therapy.
<sup>c</sup> DUXIPENT 600 mg at Week 0, followed by 300 mg every two weeks.
<sup>d</sup> Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
<sup>e</sup> Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and opthalmic herpes simplex.
<sup>f</sup> Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex ophthalmicus externus, and herpes virus infection, but excludes eczema herpeticum.
Safety through Week 52 (Trial 3)

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

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

Safety through 148 Weeks (Trial 9)

The long-term safety profile observed in this trial through 148 weeks was generally consistent with the safety profile of DUXIPENT observed in controlled studies.

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

The safety of DUXIPENT 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 DUXIPENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUXIPENT 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 DUXIPENT 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 DUXIPENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Pediatric Subjects with Atopic Dermatitis (6 to 11 Years of Age)

The safety of DUXIPENT with concomitant TCS was assessed in a trial of 367 subjects 6 to 11 years of age with moderate to severe atopic dermatitis (Trial 8). The safety profile of DUXIPENT + 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 DUXIPENT + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (Trial 9). 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 DUXIPENT + TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in Trial 8. The long-term safety profile of DUXIPENT + TCS observed in pediatric subjects was consistent with that seen in adults and adolescents with atopic dermatis [see Use in Specific Populations (6-4)].

Asthma

Adults and Adolescents (12 Years and Older)

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 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 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticos teroids 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. DUXIPENT 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 DUXIPENT 200 mg Q2W group, and 6% of the DUXIPENT 300 mg Q2W group.

Table 5 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUXIPENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 5: 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>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration (AS Trials 1, 2) and Greater than Placebo (24 Week Safety Pool)</strong></td>
<td></td>
<td></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</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
</tr>
</tbody>
</table>

a Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

b Eosinophilia = blood eosinophil ≥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.

Pediatric Subjects with Asthma (6 to 11 Years of Age)

The safety of DUXIPENT was assessed in 405 subjects 6 to 11 years of age with moderate-to-severe asthma (AS Trial 4). The safety profile of DUXIPENT in these subjects through Week 52 was similar to the safety profile from studies in adults and adolescents with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 2.2% (6 subjects) in the DUXIPENT group and 0.7% (1 subject) in the placebo group. The majority of cases were enterobiasis, reported in 1.8% (5 subjects) in the DUXIPENT group and none in the placebo group. There was one case of ascariasis in the DUXIPENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUXIPENT treatment discontinuation.

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety profile of DUXIPENT was assessed in a trial of 367 subjects with chronic rhinosinusitis with nasal polyposis (Trial 3). Concomitant therapy atopic dermatitis trial (Trial 3), keratitis was reported in 3% of the DUPIXENT group and none in the placebo group. There was one case of keratitis in the DUPIXENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUXIPENT treatment discontinuation.

Table 6: 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>CSNP Trials 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection site reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>28 (6%)</td>
</tr>
<tr>
<td><strong>Conjunctivitis</strong></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7 (2%)</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (3%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7 (2%)</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (1%)</td>
</tr>
<tr>
<td><strong>Eosinophilia</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
</tr>
<tr>
<td><strong>Toothache</strong></td>
<td></td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (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

In adult subjects with atopic dermatitis, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 subject-years) during the 16-week treatment period of the monotherapy trials (Trials 1, 2, and 4). During the 52-week treatment period of concomitant therapy 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). During the long-term OLE trial with data through 148 weeks (Trial 9), conjunctivitis was reported in 20% of the DUXIPENT group (12 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 (4 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (Trial 9), keratitis was reported in 3% of the DUXIPENT group (2 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)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUXIPENT groups in the atopic dermatitis trials. The rates remained stable through 148 weeks in the long-term OLE trial (Trial 9).

Herpes zoster was reported in <1% of the DUXIPENT groups (1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUXIPENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUXIPENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (Trial 9), 1.9% of DUXIPENT-treated subjects reported herpes zoster (0.99 per 100 subject-years of follow up). Among asthma subjects the frequency of herpes zoster was similar between DUXIPENT and placebo. Among CRSwNP subjects there were no reported cases of herpes zoster or eczema herpeticum.
Hypersensitivity Reactions

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

Eosinophils

DUPLEXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis (Trial 1, 2, and 4), the mean and median increases in blood eosinophils from baseline to Week 2 were 140 and 100 cells/μL, respectively, in adult and adolescent subjects with asthma (AS Trial 1 and 2), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 100 cells/μL, respectively. In subjects 6 to 11 years of age with asthma (AS Trial 4), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/μL, respectively. In subjects with CRSwNP (CSNP Trial 1 and 2), the mean and median increase in mean increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/μL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (>500 cells/μL) was similar in DUPLEXENT and placebo groups. Treatment-emergent eosinophilia (>5,000 cells/μL) was reported in <3% of DUPLEXENT-treated patients and <0.5% in placebo-treated patients (Trials 1, 2, 4, AS Trial 1, 2, and 4; CSNP Trial 1 and 2). Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

Cardiovascular

In the 1-year placebo controlled trial in adult and adolescent 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 DUPLEXENT 200 mg Q2W group, 4 (0.6%) of the DUPLEXENT 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 DUPLEXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPLEXENT + TCS 300 mg Q2W 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 DUPLEXENT 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 DUPLEXENT 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 (6 to 11 years of age) with atopic dermatitis who received DUPLEXENT 200 mg Q2W or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received DUPLEXENT 100 mg Q2W or 200 mg Q4W for 52 weeks.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPLEXENT 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 DUPLEXENT 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 DUPLEXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPLEXENT and placebo subjects were mostly low. In subjects who received DUPLEXENT, 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 DUPLEXENT therapy [see Warnings and Precautions (5.1)].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of DUPLEXENT. 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 DUPLEXENT.

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 DUPLEXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningooccal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningooccal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningooccal 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 DUPLEXENT during pregnancy.

Healthcare providers and patients may call 1-877-311-8972 or go to https://matherobaby.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 DUPLEXENT 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, DUPLEXENT 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 development 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. Background incidence rates have been used to estimate 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 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 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 DUPLEXENT and any potential adverse effects on the breastfed child from DUPLEXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

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

Use of DUPLEXENT in this age group is supported by Trial 6 which included 251 adolescents ages 12 to 17 years old with moderate-to-severe atop dermatitis and Trial 8 which included 367 children ages 6 to 11 years old with severe atopic dermatitis. The safety and effectiveness 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 completed Trials 6 and 8. Trial 7 included 136 adolescents from Trial 6 and 110 children from Trial 8 with moderate atop dermatitis at enrollment into the extension study. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atop dermatitis at enrollment. No new safety signals were identified in Trial 7 [see Adverse Reactions (6.1)].

Safety and effectiveness in pediatric patients ≤5 years of age with atop dermatitis have not been established.

Asthma

The safety and effectiveness of DUPLEXENT for an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPLEXENT for this indication is supported by evidence from adequate and well-controlled studies in adult and pediatric patients 6 years and older [see Clinical Studies (14.2)].
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. 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. 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.

The safety and effectiveness in pediatric patients (<6 years of age with asthma have not been established.

**CRSwNP**

CRSwNP does not normally occur in pediatric patients. Safety and effectiveness 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 DUPLEX 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 older 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 DUPLEX, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

Of the 440 subjects with CRSwNP exposed to DUPLEX, 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 DUPLEX 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.

DUPLEX (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPLEX 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 (3.5 mg), polysorbate 80 (2.3 mg), sodium acetate (1.2 mg), sucrose (57 mg), and water for injection, pH 5.9. Each 100 mg pre-filled syringe delivers 100 mg dupilumab in 0.67 mL which also contains L-arginine hydrochloride (3.5 mg), L-histidine (2.1 mg), polysorbate 80 (1.3 mg), sodium acetate (0.7 mg), sucrose (34 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 receptors. IL-4 signals via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation driven by IL-4 and IL-13 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 (i.e., histamine, eosinocid, leukotrienes, cytokines, chemokines) are involved in inflammation. Blocking IL-4Rα with dupilumab inhibits IL-4- and IL-13 mediated inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. 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 of inflammation. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and perisin were decreased relative to placebo. Reductions in these biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined 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 2 was 35% 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, and 23.7±7.4 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 either weekly (twice the recommended dosing frequency) or Q2W, 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 mcg/mL 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 monocular 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 (<8 ng/mL) were 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 or 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 39.7±21.7 mcg/mL for 200 mg administered Q2W.

#### Pediatric Patients

##### Atopic Dermatitis

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean ± SD steady-state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

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), 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.

In AS Trial 4, dupilumab pharmacokinetics was investigated in 270 patients with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 children weighing <30 kg) or 200 mg Q2W (for 179 children weighing ≥30 kg). The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight <30 kg and ≥30 kg demonstrated that steady-state trough concentrations (98.7±41.0 mcg/mL and average concentrations higher than the observed trough concentrations and average concentrations of 100 mg Q2W (<30 kg).

#### Renal or Hepatic Impairment

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

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3; NCT02277743, 02277769, and 02205086, respectively) enrolled a total of 2191 subjects: 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator’s Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were White, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33, and the baseline weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (Trials 1 and 2), subjects received DUPIXENT or placebo for 16 weeks. In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous, and genital areas for 52 weeks.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in Peak Pruritus NRS (at least a 4-point improvement in the Peak NRS from baseline to Week 16). Subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects with baseline weight of 60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. DUPIXENT 300 mg QW + Placebo was added to DUPIXENT 300 mg Q2W at Week 0, followed by 300 mg Q2W + Placebo for 16 weeks. Subjects in Trials 1 and 2 who had an IGA 0 or 1 with a reduction of ≥20% on the 0-4 IGA scale at Week 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 NRS (NRS) was 7 on a scale of 0-10.

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All three trials assessed the primary endpoint, the change from baseline to Week 16 in Peak Pruritus NRS (at least a 4-point improvement in the Peak NRS from baseline to Week 16). Subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects with baseline weight of 60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. DUPIXENT 300 mg QW + Placebo was added to DUPIXENT 300 mg Q2W at Week 0, followed by 300 mg Q2W + Placebo for 16 weeks. Subjects in Trials 1 and 2 who had an IGA 0 or 1 with a reduction of ≥20% on the 0-4 IGA scale at Week 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 NRS (NRS) was 7 on a scale of 0-10.
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 9.

### Table 9: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)*

<table>
<thead>
<tr>
<th>IGA 0 or 1 abc</th>
<th>DUPIXENT 200 mg N=84</th>
<th>Placebo N=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>24%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>IGA-75 abc</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>23%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)</td>
<td>37%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Full Analysis Set (FAS) includes all subjects randomized.
  
  a 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.
  
  b Subjects who received rescue treatment or with missing data were considered non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively).
  
  c 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.

### Figure 2: Proportion of Adolescent Subjects with ≥4-point Improvement on the Peak Pruritus NRS in Trial 6 (FAS)a

<table>
<thead>
<tr>
<th>IGA 0 or 1</th>
<th>DUPIXENT (N=82)</th>
<th>Placebo (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>13%</td>
<td>39%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>75%</td>
<td>28%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>46%</td>
<td>7%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)</td>
<td>54%</td>
<td>12%</td>
</tr>
<tr>
<td>61%</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

Full Analysis Set (FAS) includes all subjects randomized.

### Figure 3: Proportion of Pediatric Subjects with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in Trial 8 (FAS)b

<table>
<thead>
<tr>
<th>IGA 0 or 1</th>
<th>DUPIXENT 300 mg Q4W with TCS (N=61)</th>
<th>Placebo + TCS (N=61)</th>
<th>Placebo + TCS (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 kg</td>
<td>30%</td>
<td>13%</td>
<td>39%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>75%</td>
<td>28%</td>
<td>75%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>26%</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>46%</td>
<td>7%</td>
<td>36%</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)</td>
<td>54%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>61%</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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

d At Day 1, subjects received 600 mg of DUPIXENT.

e At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUPIXENT.

A greater proportion of subjects randomized to DUPIXENT + TCS achieved an improvement in the Peak Pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at Week 16). See Figure 3.

### 14.2 Asthma

The asthma development program for patients aged 12 years and older 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. 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 enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3, subjects with screening blood eosinophil level of ≥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 FEV1 (L) in subjects with baseline blood eosinophil counts ≥300 cells/mL. Other endpoints included percent change from baseline in FEV1 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 FEV1 (Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 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 optimizing 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 existing 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 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 11 below.

Table 11: 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 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 (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>
<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>

ICS = 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 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 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 0.97. 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 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 12.

Response rates by baseline blood eosinophils and FeNO for AS Trial 2 are shown for the overall population in Figure 4 and Figure 5, respectively. Elevation of FeNO can be a marker of the eosinophilic asthma phenotype when supported by clinical data. 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 (≥150 cells/mL) or FeNO (≥25 ppb). In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥150 cells/mL and FeNO ≥25 ppb, 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 12: Rate of Severe Exacerbations 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</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 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 0.97. 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 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 12.

The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in AS Trial 2 (Figure 6).
Lung Function

Significant increases in pre-bronchodilator FEV₁ were observed at Week 12 for AS Trials 1 and 2 in the analysis populations (subjects with baseline blood eosinophil count ≥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 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 vs 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 13.

Improvements in FEV₁ by baseline blood eosinophilis and baseline FeNO for AS Trial 2 are shown in Figur 7 and 8, respectively. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophilis (≥150 cells/mL) or FeNO (≥25 ppb). In subjects with baseline blood eosinophil count <150 cells/mL and FeNO<25 ppb, similar differences in FEV₁ were observed between DUPIXENT and placebo.

Mean changes in FEV₁ over time in AS Trial 2 are shown in Figure 9.

Table 13: 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></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>LS Mean Change from baseline (%)</td>
<td>LS Mean Difference vs. placebo (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AS Trial 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</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>64</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>68</td>
<td>0.18 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AS Trial 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</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>148</td>
<td>0.21 (15.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</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>142</td>
<td>0.22 (14.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-bronchodilator FEV₁, 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 66% vs 54% placebo (odds ratio 1.61; 95% CI: 1.17, 2.21) and 65% 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 ratios: 1.46; 95% CI: 0.90, 2.35) 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, 2.85), respectively.

Oral Corticosteroid Reduction (AS Trial 3)

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 82 (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 Weeks 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 corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry) Subjects were randomized to DUPIXENT (N=273) or matching placebo (N=135) every other week based on body weight <30 kg (100 mg
The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma exacerbations were 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. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV₁, percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACO-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

The demographics and baseline characteristics for AS Trial 4 are provided in Table 14 below.

Table 14: Demographics and Baseline Characteristics for AS Trial 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AS Trial 4 (N=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>% Female</td>
<td>56</td>
</tr>
<tr>
<td>% White</td>
<td>88</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>36</td>
</tr>
<tr>
<td>Mean exacerbations in previous year (± SD)</td>
<td>2.4 (2.2)</td>
</tr>
<tr>
<td>High dose ICS dose (%)</td>
<td>44</td>
</tr>
<tr>
<td>Pre-dose FEV₁ (L) at baseline (± SD)</td>
<td>1.48 (0.41)</td>
</tr>
<tr>
<td>Mean percent predicted FEV₁ (%) (±SD)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Mean % Reversibility (± SD)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall (AD %, AR %)</td>
<td>92 (36, 82)</td>
</tr>
<tr>
<td>Mean FeNO ppb (± SD)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>% patients with FeNO ppb ≥20</td>
<td>50</td>
</tr>
<tr>
<td>Median total IgE IU/mL (±SD)</td>
<td>792 (1093)</td>
</tr>
<tr>
<td>Mean baseline Eosinophil count (± SD) cells/mL</td>
<td>502 (395)</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroid; FEV₁ = Forced expiratory volume in 1 second; AD = atopic dermatitis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide.

DUPRIDENT significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in populations with an eosinophilic phenotype as indicated by elevated blood eosinophils and/or the population with elevated FeNO. Subgroup analyses for results of DUPRIDENT treatment based upon either baseline eosinophil level or baseline FeNO level were similar to the adolescent and adult trials and are described for the adult and adolescent asthma population above. In subjects with baseline blood eosinophil count ≥150 cells/mL and FeNO ≥20 ppb, similar severe asthma exacerbation rates were observed between DUPRIDENT and placebo.

Significant improvements in percent predicted pre-bronchodilator FEV₁ were observed at Week 24. Improvements were also observed for ACO-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACO-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACO-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥300 cells/mL, DUPRIDENT led to a higher proportion of subjects with a response in ACO-7-IA (80.6% versus 64.3% for placebo) with an OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

Table 15: Efficacy Results of DUPRIDENT in AS Trial 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EOS ≥300 cells/mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Severe Exacerbation Rate over 52 Weeks</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>DUPRIDENT 100 mg Q2W (&lt;30 kg)/200 mg Q2W (≥30 kg)</td>
<td>175</td>
</tr>
<tr>
<td>Placebo</td>
<td>84</td>
</tr>
<tr>
<td>Mean Change from Baseline in Percent Predicted FEV₁ at Week 12</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>LS mean Δ from Baseline</td>
</tr>
<tr>
<td>DUPRIDENT 100 mg Q2W (&lt;30 kg)/200 mg Q2W (≥30 kg)</td>
<td>168</td>
</tr>
<tr>
<td>Placebo</td>
<td>80</td>
</tr>
</tbody>
</table>

* This reflects the prespecified primary analysis population for AS Trial 4 in the United States.

Improvements were also observed for ACO-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACO-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACO-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥300 cells/mL, DUPRIDENT led to a higher proportion of subjects with a response in ACO-7-IA (80.6% versus 64.3% for placebo) with an OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

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 in bilateral endoscopic nasal polyps score (NPS, 0-8 scale) as graded by central blinded readers, and change from baseline to Week 24 in percent predicted FEV₁ (L). The secondary endpoints included mean change from baseline and responder rates in the ACO-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

The demographics and baseline characteristics for these 2 trials are provided in Table 16 below.
Table 16: 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 0-110</td>
<td>49.4 (20.2)</td>
<td>51.9 (20.9)</td>
</tr>
<tr>
<td>Mean blood eosinophils (cells/mcL) (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</td>
<td>% Overall</td>
<td>75</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

Table 17: Results of the Primary Endpoints in CRSwNP Trials

<table>
<thead>
<tr>
<th>Primary Endpoints at Week 24</th>
<th>Placebo (n=133)</th>
<th>DUPIXENT 300 mg Q2W (n=143)</th>
<th>LS mean difference vs. Placebo (95% CI)</th>
<th>Placebo (n=153)</th>
<th>DUPIXENT 300 mg Q2W (n=295)</th>
<th>LS mean difference vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scores</td>
<td>Baseline mean</td>
<td>LS mean change</td>
<td>Baseline mean</td>
<td>Baseline mean</td>
<td>LS mean change</td>
<td>Baseline mean</td>
</tr>
<tr>
<td>NPS</td>
<td>5.86</td>
<td>0.17</td>
<td>5.64</td>
<td>1.89</td>
<td>2.06</td>
<td>(-2.43, -1.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.96</td>
<td>0.10</td>
<td>6.18</td>
</tr>
<tr>
<td>NC</td>
<td>2.45</td>
<td>-0.45</td>
<td>2.26</td>
<td>-1.34</td>
<td>-0.89</td>
<td>(-1.07, -0.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.38</td>
<td>-0.38</td>
<td>2.46</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 11).

Figure 11: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in CSNP Trial 2 - ITT Population

Figure 12: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 48 in CSNP Trial 1 - ITT Population

At Week 52, the LS mean difference for nasal congestion in the DUXIXENT group versus placebo was -0.98 (95% CI: -1.17, -0.79). In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the DUXIXENT group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score in the DUXIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in CSNP Trial 1 and -5.13 (95% CI: -5.80, -4.46) in CSNP Trial 2. At Week 52, in CSNP Trial 2 the LS mean difference for LMK sinus CT scan score in the DUXIXENT group versus placebo was -6.94 (95% CI: 7.87, -6.01). Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUXIXENT group versus placebo was -1.12
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 (dupilumab) 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.

The pre-filled syringe with needle shield is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5914-00)
- 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00)
- 100 mg of DUPIXENT in 0.67 mL solution (NDC 0024-5911-00)

The pre-filled pen is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00)
- 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>
<th>100 mg/0.67 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>
<td>NDC 0024-5911-02</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>

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, 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.
What is DUPIXENT?
DUPIXENT® (DU-pix-ent)
(dupilumab)
injection, for subcutaneous use

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 6 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 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 or asthma under 6 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 (hypsersensitivity), 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
• **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:
  - rash
  - shortness of breath
  - 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)
• parasitic (helminth) infections

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. Call 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)

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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: October 2021