נובמבר 2022

DUPIXENT 300mg solution for injection
DUPIXENT 200mg solution for injection

חומר פעיל: dupilumab 300mg/2ml (150 mg/ml)
חומר פעיל: dupilumab 200mg/1.14ml (175 mg/ml)

חברת סאנופי אוונטיס מבקשת לעדכן שאושרה הרחבת הטיפול באסתמה לילדים מגיל 6 שנים ומעלה.

כמו כן אושרו לתכשירים עטי הזרקה, שיתווספו למזרקים המשווקים.

משטר המינון והעלונים התעדכנו בהתאם.

להלן התוויות התכשירים המאושרות עבור שני התכשירים:

Atopic Dermatitis
DUPIXENT is 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.

Asthma
DUPIXENT is indicated as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.
Limitation of Use:
DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

התוויה נוספת מאושרת עבור התכשיר **Dupixent 300mg**:

Chronic Rhinosinusitis with Nasal Polyposis
DUPIXENT 300mg is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

מצורפים העלונים העדכניים מתאריך אוקטובר 2022: עלון לרופא, עלון לצרכן עבור דופיקסנט 200 מ"ג ועלון לצרכן עבור דופיקסנט 300 מ"ג.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום - סאנופי-אוונטיס ישראל בע"מ, רח' בני גאון 10 נתניה או בטלפון: 09-8633700 .

להלן הקישור לאתר משרד הבריאות: https://www.gov.il/he/service/israeli-drug-index

בברכה,
חברת סאנופי-אוונטיס ישראל בע"מ

העדכונים העיקריים **בעלון לרופא** הינם:

2. THERAPEUTIC INDICATIONS

DUPIXENT is indicated for the following diseases:

2.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

2.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment ~~in~~ of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma ~~aged 12 years and older~~ characterized by ~~with~~ an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

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

2.3 Chronic Rhinosinusitis with Nasal Polyposis

DUPIXENT 300mg is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

~~1.~~ 3. DOSAGE AND ADMINISTRATION

3.1 Important Administration Instructions

DUPIXENT is administered by subcutaneous injection.

DUPIXENT is intended for use under the guidance of a healthcare provider. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".

Use of Pre-filled Pen or Pre-filled Syringe

The DUPIXENT pre-filled pen is for use in adult and pediatric patients aged 12 years and older.

The DUPIXENT pre-filled syringe is for use in adult and pediatric patients aged 6 years and older.

A caregiver or patient 12 years of age and older may inject DUPIXENT using the pre-filled syringe or pre-filled pen. In pediatric patients 12 to 17 years of age, administer DUPIXENT under the supervision of an adult.

In pediatric patients 6 years to 11 years of age, administer DUPIXENT pre-filled syringe by a caregiver.

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3.4 Recommended Dosage for Asthma

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

- ~~an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or~~
- ~~an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week~~
- ~~for patients with oral corticosteroids dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week~~

Dosage in Adult and Pediatric Patients 12 Years and Older

The recommended dosage of DUPIXENT for adult and pediatric patients 12 years of age and older is specified in Table 2.

Table 2: Dosage of DUPIXENT in Adult and Pediatric Patients 12 Years and Older with Asthma

Initial Loading Dose	Subsequent Dose
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
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)

Dosage in Pediatric Patients 6 to 11 Years of Age

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

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

Body Weight	Initial[a] and Subsequent Doses
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

[a] For pediatric patients 6 to 11 years of age with asthma, no initial loading dose is recommended.

For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe AD, follow the recommended dosage as per Table 1 which includes an initial loading dose.

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5. WARNINGS AND PRECAUTIONS

56.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (76.1, 76.2, 76.3)]*.

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56.8 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections.

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. 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)]*.

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Pediatric Subjects 6 to 11 Years of Age with Asthma

The safety of DUPIXENT was assessed in 405 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma (VOYAGE). The safety profile of DUPIXENT in these subjects through Week 52 was similar to the safety profile from studies in adult and pediatric subjects 12 years of age and older with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 2.2% (6 subjects) in the DUPIXENT group and 0.7% (1 subject) in the placebo group. The majority of cases were enterobiasis, reported in 1.8% (5 subjects) in the DUPIXENT group and none in the placebo group. There was one case of ascariasis in the DUPIXENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUPIXENT treatment discontinuation.

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Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included anaphylaxis, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum and erythema mutiforme *[see Contraindications (4~~5~~), Warnings and Precautions (5~~6~~.1), and Adverse Reactions (6~~7~~.2)]*.

Eosinophils

DUPIXENT-treated subjects with AD ~~atopic dermatitis~~, asthma and CRSwNP had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In adult subjects with AD ~~atopic dermatitis~~ (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively.

In adult and pediatric subjects 12 years of age and older with asthma (DRI12544 and QUEST), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mcL, respectively.

In adult subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across the trials for AD ~~atopic dermatitis~~, asthma and CRSwNP indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups.

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <3 ~~2~~% of DUPIXENT-treated subjects and <0.5% in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DRI12544, QUEST, and VOYAGE; ~~and~~ SINUS-24 and SINUS-52). Blood eosinophil counts declined to near baseline levels during study treatment. In study AD-1539, treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8% of DUPIXENT-treated subjects and 0% in placebo treated subjects *[see Warnings and Precautions (5~~6~~.3)]*.

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67.2 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 DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies.~~

Atopic Dermatitis

Approximately 6% of subjects with AD who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 to 11 years of age with atopic dermatitis who received DUPIXENT 200 mg Q2W or 300 mg Q4W for 16 weeks.

Approximately 16% of pediatric subjects 12 to 17 years of age with AD ~~atopic dermatitis~~ who received DUPIXENT ~~dupilumab~~; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Asthma

Approximately 5% of subjects with asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; 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 asthma who received either DUPIXENT 100 mg Q2W or 200 mg Q2W up to 52 weeks.

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

~~Regardless of age or population, up to 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.~~

~~Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.~~

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Chronic Rhinosinusitis with Nasal Polyposis

Approximately 5% of subjects with CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 3% had neutralizing antibodies.

The antibody titers detected in subjects who received ~~both~~ DUPIXENT ~~and placebo subjects~~ were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to DUPIXENT ~~dupilumab~~ was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (10~~.~~3)]*. Two adult subjects with AD who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5~~.~~6.1)]*.

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Use in Specific Populations ###### Pediatric Use

Asthma

The safety and effectiveness of DUPIXENT 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 DUPIXENT 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 (12.2)]*.

Pediatric Subjects 12 to 17 Years of Age:

A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST 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 pediatric subjects 12 to 17 years of age and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults.

~~Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established.~~

Dupilumab exposure was higher in pediatric subjects 12 to 17 years of age than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (10~~.~~3)]*.

The adverse event profile in pediatric subjects 12 to 17 years of age was generally similar to the adults *[see Adverse Reactions (6~~.~~1)]*.

Pediatric Subjects 6 to 11 Years of Age:

A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated *[see Clinical Studies (12.2)]*. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W *[see Clinical Pharmacology (10.3)]*. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14424). Eighteen subjects (≥15 to <30 kg) out of 365 subjects were exposed to 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric AD indication *[see Adverse Reactions (6.1) and Clinical Pharmacology (10.3)]*.

Safety and effectiveness in pediatric patients younger than 6 years of age with asthma have not been established.

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