ספטמבר 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)

הטיפול באטופיק דרמטיטיס הורחב לילדים מגיל 6 שנים ומעלה. משטר המינון התעדכן 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 in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

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

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).

חברת סאנופי אוונטיס מבקשת להודיע על עדכון העלון לרופא והעלונים לצרכן באוגוסט 2022.

מצורפים העלונים העדכניים.

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

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 ~~12~~ 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.

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3. DOSAGE AND ADMINISTRATION

3.1 Important Administration Instructions

DUPIXENT is administered by subcutaneous injection.

~~Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated.~~

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 Syringe

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

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.

Administration Instructions

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 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.

The DUPIXENT "Instructions for Use" contains more detailed instructions on the preparation and administration of DUPIXENT.

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3.2 Vaccination Prior to Treatment

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT [see Warnings and Precautions (6.9)].

3.3 Recommended Dosage for Atopic Dermatitis

Dosing in Adults

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

~~Dosing in Adolescents~~ Dosage in Pediatric Patients 6 Years to 17 Years of Age

~~The recommended dose of DUPIXENT for patients 12 to 17 years of age is specified in Table 1.~~

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

Table 1: ~~**Dose of DUPIXENT for Subcutaneous Administration in Adolescent Patients**~~ **Dosage of DUPIXENT in Pediatric Patients 6 Years to 17 Years of Age with Atopic Dermatitis**

Body Weight	Initial Dose Initial Loading Dose	~~Subsequent Doses (every other week)~~ Subsequent Dosage
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg every 4 weeks (Q4W)
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)
~~less than 60 kg~~	~~400 mg (two 200 mg injections)~~	~~200 mg~~
60 kg or more	600 mg (two 300 mg injections)	~~300 mg~~ 300 mg every other week (Q2W)

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3.6 Missed dose

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

Special populations

Elderly (≥ 65 years)
No dose adjustment is recommended for elderly patients.

Renal impairment
No dose adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment.

Hepatic impairment
No data are available in patients with hepatic impairment.

Body weight
No dose adjustment for body weight is recommended for patients with asthma 12 years of age and older or in adults with atopic dermatitis.

Paediatric patients
The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established. No data are available.

The safety and efficacy of dupilumab in children with severe asthma below the age of 12 years have not been established. No data are available.

Method of administration

Subcutaneous use

Dupilumab is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.

For the initial 400 mg dose, two 200 mg injections should be administered consecutively in different injection sites.

For the initial 600 mg dose, two 300 mg injections should be administered consecutively in different injection sites.

It is recommended to rotate the injection site with each injection. Dupilumab should not be injected into skin that is tender, damaged or has bruises or scars.

A patient may self inject dupilumab or the patient's caregiver may administer dupilumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use (IFU) section in the package leaflet.

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6. WARNINGS AND PRECAUTIONS

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6.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials.

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT 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 (7.1)]*.

Among subjects with asthma ~~subjects~~, the frequencies of conjunctivitis and keratitis were similar between DUPIXENT and placebo *[see Adverse Reactions (7.1)]*.

~~In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT 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 (7.1)]*.~~

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis patients. Some patients reported visual disturbances (e.g., blurred vision) associated with conjunctivitis or keratitis.

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

Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate *[see Adverse Reactions (7.1)]*.

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7. ADVERSE REACTIONS

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Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 367 pediatric subjects 6 to 11 years of age with severe atopic dermatitis (AD-1652). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adult and pediatric subjects 12 to 17 years of age with atopic dermatitis. The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 368 pediatric subjects 6 to 11 years of age with atopic dermatitis (AD-1434). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe atopic dermatitis at the time of enrollment in AD-1434. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD1652. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 to 11 years of age was consistent with that seen in adult and pediatric subjects 12 to 17 years of age with atopic dermatitis [see Use in Specific Populations (8.3)].

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8. USE IN SPECIFIC POPULATIONS

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8.3 Pediatric Use

Atopic Dermatitis

The safety and effectiveness of DUPIXENT have been established in pediatric patients 6 ~~12~~ years of age and older with moderate-to-severe atopic dermatitis.

Use of DUPIXENT in this age group is supported by data from the following clinical trials:

- AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-tosevere atopic dermatitis treated with DUPIXENT
- AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe atopic dermatitis treated with DUPIXENT + TCS

The safety and efficacy were generally consistent between pediatric and adult patients [see Adverse Reactions (7.1) and Clinical Studies (14.1)].

Use[HG/1] is also supported by AD-1434, an open-label extension study that enrolled subjects who completed Trials AD-1526 and AD-1652 . AD-1434 included 136 adolescents from Trial AD-1434 and 110 children from Trial AD-1652 with moderate atopic dermatitis at enrollment into the extension study. Trial AD-1434 included 64 adolescents from Trial AD-1526 and 72 children from AD-1652 with severe atopic dermatitis at enrollment. No new safety signals were identified in AD-1434 [see Adverse Reactions (7.1)].

~~Use of DUPIXENT in this age group is supported by AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate to severe atopic dermatitis were enrolled in Trial 6. The safety and effectiveness were generally consistent between pediatric and adult patients *[see Adverse Reactions (7.1) and Clinical Studies (14.1)]*.~~

DUPIXENT is not indicated ~~safety and effectiveness~~ in pediatric patients (<6 ~~12~~ years of age) with atopic dermatitis. ~~have not been established.~~

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11.3 Pharmacokinetics

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Pediatric Patients

Atopic Dermatitis

For pediatric subjects12 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 pediatric subjects 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.

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13. CLINICAL STUDIES

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Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

Subjects in the DUPIXENT Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the DUPIXENT Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of ≥30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1652, the mean age was 8.5 years, the median weight was 29.8 kg, 50% of subjects were female, 69% were White, 17% were Black, and 8% were Asian. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at 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).

Table 8 presents the results by baseline weight strata for the approved dose regimens.

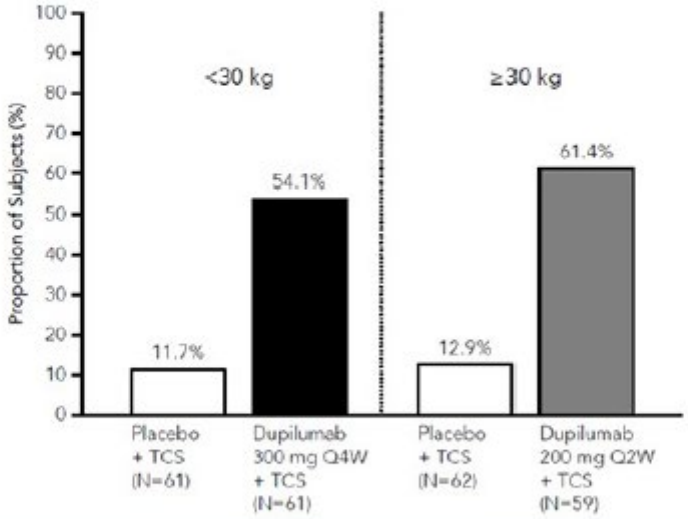
Table 8: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)[a] in Pediatric Subjects 6 to 11 Years of Age with AD

	DUPIXENT 300 mg Q4W[d] + TCS (N=61)	Placebo + TCS (N=61)	DUPIXENT 200 mg Q2W[e] + TCS (N=59)	Placebo + TCS (N=62)
	<30 kg	<30 kg	≥30 kg	≥30 kg
IGA 0 or 1[b,c]	30%	13%	39%	10%
EASI-75[c]	75%	28%	75%	26%
EASI-90[c]	46%	7%	36%	8%
Peak Pruritus NRS (≥4-point improvement)[c]	54%	12%	61%	13%

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear").
[c] Subjects who received rescue treatment or with missing data were considered as 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.

Figure 3: Proportion of Pediatric Subjects 6 to 11 Years of Age with AD with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in AD-1652a (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomized.

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העדכונים העיקריים **בעלונים לצרכן** מובאים כדוגמא מעלון ה- 300 מ"ג והינם:

1. למה מיועדת התרופה?

דופיקסנט 300 מ"ג משמשת לטיפול במבוגרים וילדים ~~מתבגרים~~ מגיל 6 ~~12~~ שנים ומעלה במצבים הבאים:	
דלקת עור אטופית בדרגת חומרה בינונית עד קשה, כאשר המחלה אינה מווסתת בצורה מספקת בעזרת תרופות מרשם לטיפול מקומי בעור או כאשר המטופל לא יכול להשתמש בטיפול מקומי. ניתן להשתמש בדופיקסנט עם או בלי קורטיקוסטרואידים לטיפול מקומי.	
דופיקסנט 300 מ"ג משמשת לטיפול במבוגרים וילדים מגיל 12 שנים ומעלה במצבים הבאים:	
טיפול אחזקה באסתמה בדרגת חומרה בינונית עד קשה בשילוב עם תרופות נוספות לטיפול באסתמה אצל מטופלים שהאסתמה שלהם אינה נשלטת בעזרת התרופות שהם מקבלים לאסתמה. דופיקסנט עוזרת למנוע התקפי אסתמה חמורים ויכולה לשפר את הנשימה. דופיקסנט עשויה גם לעזור להפחית את כמות הקורטיקוסטרואידים במתן אוראלי (בליעה), שהמטופל נוטל תוך מניעת התקפי אסתמה חמורים ושיפור הנשימה. דופיקסנט אינה משמשת לטיפול בבעיות נשימה פתאומיות.	
דופיקסנט 300 מ"ג משמשת בשילוב עם תרופות נוספות בכדי לטפל במחלת כרונית עם פוליפוזיס באף במבוגרים שמחלתם אינה נמצאת בשליטה.	

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2. לפני השימוש בתרופה

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ילדים ומתבגרים
התרופה אינה מיועדת לטיפול בדלקת עור אטופית בילדים מתחת לגיל 6 שנים.
התרופה אינה מיועדת לטיפול בבאסתמה בילדים מתחת לגיל 12 שנים.
התרופה אינה מיועדת לטיפול בנמלת כרונית עם פוליפוזיס באף בילדים ומתבגרים מתחת לגיל 18 שנים.

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3. כיצד תשתמש בתרופה?

קרא היטב את "הוראות השימוש" המצורפות לעלון לצורך קבלת מידע כיצד להכין ולהזריק דופיקסנט וכיצד לאחסן את התרופה בצורה נכונה ומן כיצד להשליך מזרקי דופיקסנט משומשים.

יש להשתמש בתרופה תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתרופה.

דופיקסנט ניתנת בזריקה מתחת לעור (זריקה תת עורית).
אם אתה הרופא או האחות שלך מחליטים שאתה או המטפל שלך יכולים לתת את זריקת הדופיקסנט, אתה או המטפל שלך צריכים לקבל הדרכה על הדרך הנכונה להכין ולבצע את ההזרקה צריכים להחליט אם אתה צריך להזריק דופיקסנט בעצמך.

אל תנסה להזריק הזרק דופיקסנט בעצמך לפני שתקבל רק אחרי שתקבל הדרכה מהרופא או מהאחות. גם אדם המטפל בך יכול לתת לך את זריקת הדופיקסנט שלך לאחר קבלת הדרכה מתאימה.

עבור ילדים ומתבגרים מגיל 12 שנים ומעלה, מומלץ שזריקת דופיקסנט תינתן על ידי מבוגר או תחת פיקוחו. עבור ילדים צעירים מתחת לגיל 12 שנים, זריקת דופיקסנט צריכה להינתן על ידי מטפל.

כל מזרק של דופיקסנט 300 מ"ג מכיל מנה אחת של דופיקסנט (300 מ"ג).

אין לנער את המזרק.

קרא היטב את "הוראות השימוש" של המזרק לפני השימוש בדופיקסנט.

כמה דופיקסנט להזריק ולמשך כמה זמן
המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.
כל מזרק של דופיקסנט 300 מ"ג מכיל מנה אחת של דופיקסנט (300 מ"ג).
עבור ילדים ומתבגרים מגיל 12 שנים ומעלה, מומלץ שזריקת דופיקסנט תינתן על ידי מבוגר או תחת פיקוחו.
המנה הראשונית המקובלת בדרך כלל היא שתי זריקות ואחר כך זריקה אחת כל שבועיים או כל 4 שבועות, בהזרקה תת עורית.
אין לעבור על המנה המומלצת.

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4. תופעות לוואי

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תופעות הלוואי השכיחות ביותר:

- תגובות באתר ההזרקה
- דלקת בעיניים ובעפעפיים, כולל אדמומיות, נפיחות וגירוד, לפעמים עם ראייה מטושטשת.
- כאב גרון (כאב בלוע)
- פצעי קור בפה ובשפתיים
- ספירה גבוהה של תאי דם לבנים מסוימים (אאוזינופיליה)
- קשיים בשינה
- כאב שיניים
- דלקת בקיבה
- כאבי מפרקים
- זיהומים טפיליים במע'

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בברכה,
חברת סאנופי-אוונטיס ישראל בע"מ