Professional Information for DUPIXENT 200 mg / 300 mg

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DUPIXENT 200 mg solution for injection

DUPIXENT 300 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DUPIXENT 200 mg solution for injection

Each single-use pre-filled syringe with needle shield contains 200 mg dupilumab in 1,14 mL solution (175 mg/mL).

Contains sugar (57 mg sucrose per 1,14 mL solution).

DUPIXENT 300 mg solution for injection

Each single-use pre-filled syringe with needle shield contains 300 mg dupilumab in 2 mL solution (150 mg/mL).

Each single-use pre-filled syringe contains 300 mg dupilumab in 2 mL solution (150 mg/mL).

Contains sugar (100 mg sucrose per 2 mL solution).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

DUPIXENT is supplied as a sterile, preservative-free, clear to slightly opalescent, colourless to pale yellow solution for subcutaneous injection, with no visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUPIXENT is indicated for the following type 2 inflammatory diseases:

ATOPIC DERMATITIS

DUPIXENT is indicated for the treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical corticosteroid therapies or when those therapies are not advisable.

DUPIXENT can be used with or without additional topical corticosteroids therapy.

ASTHMA

DUPIXENT is indicated in patients 6 years and older as an add-on maintenance treatment for moderate-to-severe asthma with type 2 inflammation characterised by elevated blood eosinophils and/or elevated fractional exhaled nitric oxide (FeNO).

DUPIXENT is indicated as maintenance therapy to improve lung function.

DUPIXENT is indicated as maintenance therapy for oral corticosteroid-dependent asthma irrespective of baseline levels of type 2 inflammatory biomarkers.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

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

DUPIXENT is indicated to reduce the need for surgery and systemic corticosteroid use in adult patients with inadequately controlled severe CRSwNP.

DUPIXENT is indicated as an add-on maintenance treatment of co-morbid asthma in adult patients with inadequately controlled severe CRSwNP.

PRURIGO NODULARIS

DUPIXENT is indicated for the treatment of adult patients with prurigo nodularis (PN)

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.

4.2 Posology and method of administration

Posology

DUPIXENT is administered by subcutaneous injection.

ATOPIC DERMATITIS

Adults

The recommended 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.

Based on individual therapeutic response, the dosage may be increased to 300 mg given weekly.

Paediatric and adolescent patients (6 to 17 years of age)

The recommended dose of DUPIXENT for paediatric and adolescent patients 6 to 17 years of age is specified in **Table 1**.

Table 1: Dose of DUPIXENT for subcutaneous administration in paediatric and adolescent patients 6 to 17 years of age with atopic dermatitis

Body weight	Initial dose	Subsequent doses
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)
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

Paediatric patients (6 months to 5 years of age)

The recommended dose of DUPIXENT for children 6 months to 5 years of age is specified in **Table 2**.

Table 2: Dose of DUPIXENT for subcutaneous administration in paediatric patients 6 months to 5 years of age with atopic dermatitis

Body weight	Initial dose	Subsequent doses
5 to less than 15 kg	200 mg (one 200 mg injection)	200 mg every 4 weeks (Q4W)
15 to less than 30 kg	300 mg (one 300 mg injection)	300 mg every 4 weeks (Q4W)

DUPIXENT can be used with or without topical therapy.

ASTHMA

Adults and adolescents (12 years of age and older)

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. The dose may be increased to 300 mg every other week based on the prescriber's assessment.
- An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis for which DUPIXENT is indicated.

Paediatric patients (6 to 11 years of age)

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

Table 3: Dose of DUPIXENT for subcutaneous administration in paediatric patients 6 to 11 years of age with asthma

Body weight	Initial and subsequent doses
15 to less than 30 kg	300 mg every 4 weeks (Q4W)
30 to less than 60 kg	200 mg every other week (Q2W) or 300 mg every 4 weeks (Q4W)
60 kg or more	200 mg every other week (Q2W)

For paediatric patients (6 – 11 years old) with asthma and co-morbid moderate-to-severe atopic dermatitis, the recommended dose in **Table 1** should be followed.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

The recommended dose of DUPIXENT for adult patients is an initial dose of 300 mg followed by 300 mg given every other week.

PRURIGO NODULARIS

The recommended 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.

Missed dose

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

If an every other week dose is missed, 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, wait until the next dose on the original schedule.

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

Special populations

Elderly patients

No dose adjustment is recommended for elderly patients (see section 5.2).

Hepatic impairment

No data are available in patients with hepatic impairment (see section 5.2).

Renal impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see section 5.2).

Body weight

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

For patients 6 to 17 years of age with atopic dermatitis, the recommended doses are 300 mg Q4W (15 kg to < 30 kg), 200 mg Q2W (30 kg to < 60 kg) and 300 mg Q2W (≥ 60 kg).

For patients 6 months to 5 years of age with atopic dermatitis, the recommended dose is 200 mg Q4W (5 kg to < 15 kg) and 300 mg Q4W (15 kg to < 30 kg).

For patients 6 to 11 years of age with asthma, the recommended doses are 300 mg Q4W (≥ 15 kg to < 30 kg), 200 mg Q2W or 300 mg Q4W (≥ 30 kg to < 60 kg) and 200 mg Q2W (≥ 60 kg).

Paediatric population

Atopic dermatitis

Safety and efficacy in paediatric patients with atopic dermatitis younger than 6 months have not

been established (see section 5.2).

Asthma

Safety and efficacy in paediatric patients with asthma younger than 6 years have not been established (see section 5.2).

Chronic rhinosinusitis with nasal polyposis

CRSwNP does not normally occur in children. Safety and efficacy in paediatric patients with CRSwNP younger than 18 years have not been established (see section 5.2).

Prurigo nodularis

PN rarely occurs in children. Safety and efficacy in paediatric patients with PN younger than 18 years have not been established (see section 5.2).

Method of administration

Subcutaneous use.

For atopic dermatitis, asthma and prurigo nodularis patients, for the initial 600 mg dose, administer two 300 mg DUPIXENT injections subcutaneously at two different injection sites.

For atopic dermatitis and asthma patients, for the initial 400 mg dose, administer two 200 mg DUPIXENT injections subcutaneously at two different injection sites.

DUPIXENT is intended for use under the guidance of a health care professional. A patient may self-inject DUPIXENT, or the patient's caregiver may administer DUPIXENT. In children 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult.

In children 6 months to less than 12 years of age, DUPIXENT should be given by a caregiver.

Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the INSTRUCTIONS FOR USE.

The 200 mg pre-filled syringe with a needle shield should be allowed to reach room temperature by waiting for 30 minutes before injecting DUPIXENT.
The 300 mg pre-filled syringe with a needle shield or pre-filled syringe should be allowed to reach room temperature by waiting for 45 minutes before injecting DUPIXENT.

DUPIXENT is self-administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel, using a single-use pre-filled syringe. If somebody else administers the injection, the upper arm can also be used.

It is recommended to rotate the injection site with each injection.

DUPIXENT should not be injected into skin that is tender, damaged or has bruises or scars.

Special handling conditions

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration. If the solution is discoloured or contains visible particulate matter, the solution should not be used.
See section 6.4.

4.3 Contraindications

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients (see sections 4.4 and 6.1).

4.4 Special warnings and precautions for use

DUPIXENT is for subcutaneous administration only.

Hypersensitivity

If a systemic hypersensitivity reaction occurs, administration of DUPIXENT should be discontinued immediately and appropriate therapy initiated. Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions and angioedema, have been reported in clinical trials following the administration of DUPIXENT (see section 4.8).

Conjunctivitis- and keratitis-related events

Conjunctivitis- and keratitis-related events have been reported with DUPIXENT, predominantly in atopic dermatitis patients. Some patients reported visual disturbances (e.g. blurred vision) associated with conjunctivitis or keratitis (see section 4.8). Patients should report new onset or worsening eye symptoms to their health care professional. Patients treated with DUPIXENT who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination, as appropriate (see section 4.8).

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 usually, but not always, may be associated with the reduction of oral corticosteroid therapy. Medical practitioners 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 programme and cases of vasculitis consistent with eosinophilic

granulomatosis with polyangiitis (EGPA) have been reported with DUPIXENT in adult patients who participated in the asthma development programme as well as in adult patients with co-morbid asthma in the CRSwNP development programme. A causal association between DUPIXENT and these conditions has not been established.

Acute asthma symptoms or deteriorating disease

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

Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus.

Reduction of corticosteroid dosage

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

Helminth infection

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 DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until infection resolves. Enterobiasis was reported as adverse reaction in children 6 to 11 years old who participated in the paediatric asthma development programme.

Concomitant atopic conditions

Patients with co-morbid asthma should be advised not to adjust their treatment without consultation with their health care professional. When discontinuing DUPIXENT consider the potential

effects on other atopic conditions.

Sodium content

Both DUPIXENT 200 mg and DUPIXENT 300 mg contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Live vaccines

DUPIXENT has not been studied with live attenuated vaccines.

Non-live vaccines

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent) and a meningococcal polysaccharide vaccine (T cell-dependent), and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

CYP450 substrates

In a clinical trial of AD patients, the effects of dupilumab on the pharmacokinetics (PK) of CYP substrates was evaluated. The data gathered from this study did not indicate a clinically relevant effect of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6 or CYP2C9 activity.

Use with other medicines for treatment of asthma

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Due to the lack of data, the use of DUPIXENT is not recommended during pregnancy.

Lactation

It is unknown whether dupilumab is excreted in human milk. Because many antibodies are excreted in human milk, mothers receiving DUPIXENT are advised not to breastfeed their infants.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

DUPIXENT has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

ATOPIC DERMATITIS

Adults

In the overall exposure pool, a total of 2 526 patients with atopic dermatitis were treated with DUPIXENT in controlled and uncontrolled clinical trials. Of these, 739 patients were exposed for at least 1 year.

The safety of DUPIXENT monotherapy was evaluated through Week 16 based on data from three randomised, double-blind, placebo-controlled multicentre studies (SOLO 1, SOLO 2 and a phase 2, dose-ranging study) that included 1 564 adult patients with moderate-to-severe atopic dermatitis (AD).

The safety of DUPIXENT with concomitant topical corticosteroids (TCS) was evaluated based on data from one randomised, double-blind, placebo-controlled, multicentre study (CHRONOS). A total of 740 patients were treated up to 52 weeks.

Table 4 summarises the adverse reactions that occurred in ≥ 1 % of patients treated with DUPIXENT during the first 16 weeks of treatment in placebo-controlled trials.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥ 10 %); common (≥ 1 % and < 10 %); uncommon (≥ 0,1 % and < 1 %); rare (≥ 0,01 % and < 0,1 %); very rare (< 0,01 %); not known (cannot be estimated from available data).

Table 4: Adverse reactions occurring in ≥ 1 % of patients with atopic dermatitis treated with DUPIXENT through Week 16 in placebo-controlled trials

MedDRA system organ class	Frequency	Adverse reaction
Infections and infestations	Common	Conjunctivitis Oral herpes Bacterial conjunctivitis Herpes simplex
Blood and lymphatic system disorders	Common	Eosinophilia
Eye disorders	Common	Allergic conjunctivitis Eye pruritus Blepharitis Dry eye
General disorders and administration site conditions	Very common	Injection site reactions

The safety profile of DUPIXENT + TCS in adult atopic dermatitis patients through Week 52 is consistent with the safety profile observed at Week 16.

In a phase 3, multicentre, open label extension (OLE) study (AD-1225), the long-term safety of repeat doses of DUPIXENT was assessed in adults with moderate-to-severe AD who had previously participated in controlled studies of DUPIXENT or had been screened for a phase 3 study (SOLO1 or SOLO2). The safety data in AD-1225 reflect the exposure to DUPIXENT in 2 677 adult atopic dermatitis patients, including 2 254 who completed at least 52 weeks, 1 224 who completed at least 100 weeks, 561 who completed at least 148 weeks and 179 who completed at least 260 weeks of the study. The majority of the patients in Trial 5 (99,7 %) were exposed to DUPIXENT 300 mg weekly dosing (QW). The long-term safety profile observed in this study up to 5 years was generally consistent with the safety profile of DUPIXENT observed in controlled studies.

Adolescents (12 to 17 years of age)

The safety of DUPIXENT was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of DUPIXENT in these patients followed through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of DUPIXENT in patients followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1526 study. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Paediatric patients (6 to 11 years of age)

The safety of DUPIXENT was assessed in a trial of 367 patients 6 to 11 years of age with severe atopic dermatitis (AD-1652). The safety profile of DUPIXENT + TCS in these patients through Week 16 was similar to the safety profile from studies in adults and adolescents with atopic dermatitis.

The long-term safety of DUPIXENT + TCS was assessed in an open-label extension study of 368 patients 6 to 11 years of age with atopic dermatitis (AD-1434). Among patients who entered this study, 110 (29,9 %) had moderate and 72 (19,6 %) had severe atopic dermatitis at the time of enrolment in study AD-1434. The safety profile of DUPIXENT + TCS in patients followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1652. The long-term safety profile of DUPIXENT + TCS observed in paediatric patients was consistent with that seen in adults and adolescents with atopic dermatitis.

Paediatric patients (6 months to 5 years of age)

The safety of DUPIXENT + TCS was assessed in a study of 161 patients 6 months to 5 years of age with moderate-to-severe atopic dermatitis (AD-1539). The safety profile of DUPIXENT + TCS in these patients through Week 16 was similar to the safety profile from studies in adults and paediatric patients 6 to 17 years of age with atopic dermatitis.

The long-term safety of DUPIXENT + TCS was assessed in an open-label extension study of 180 patients 6 months to 5 years of age with atopic dermatitis (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 AD-1539. The long-term safety profile of DUPIXENT + TCS observed in paediatric subjects 6 months to 5 years of age was consistent with that seen in adults and paediatric patients 6 to 17 years old with atopic dermatitis.

ASTHMA

A total of 2 888 adult and adolescent patients with moderate-to-severe asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (DRI12544, QUEST and VENTURE). Of these, 2 678 had a history of 1 or more severe exacerbations in the year prior to enrolment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 patients with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE). DUPIXENT 200 mg or 300 mg was administered subcutaneously every other week, following an initial dose of 400 mg or 600 mg, respectively.

In DRI12544 and QUEST studies, the proportion of patients who discontinued treatment due to adverse events was 3,2 % of the DUPIXENT 200 mg Q2W group and 6,1 % of the DUPIXENT 300 mg Q2W group.

Table 5 summarises the adverse reactions that occurred at a rate of at least 3 % of patients treated with DUPIXENT and at higher rate than in their respective comparator groups in DRI12544 and QUEST studies.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥ 10 %); common (≥ 1 % and < 10 %); uncommon (≥ 0,1 % and < 1 %); rare (≥ 0,01 % and < 0,1 %); very rare (< 0,01 %); not known (cannot be estimated from available data).

Table 5: Adverse reactions occurring in ≥ 3 % of the DUPIXENT groups in the DRI12544 and QUEST

MedDRA system organ class	Frequency	Adverse reaction
General disorders and administration site conditions	Very common Common	Injection site erythema Injection site oedema

		Injection site pruritus

Adults and adolescents (12 years and older)

The long-term safety of DUPIXENT was assessed in an open-label extension study in 2 282 patients 12 years and older with moderate-to-severe asthma (TRAVERSE). In this study, patients were followed for up to 96 weeks, resulting in 3 169 patient-years cumulative exposure to DUPIXENT. The safety profile of DUPIXENT in TRAVERSE was consistent with the safety profile observed in pivotal asthma studies for up to 52 weeks of treatment.

Paediatric patients (6 to 11 years of age)

The safety of DUPIXENT was assessed in 405 patients 6 to 11 years of age with moderate-to-severe asthma (VOYAGE). The safety profile of DUPIXENT in these patients through Week 52 was similar to the safety profile from studies in adults and adolescents with moderate-to-severe asthma, with the additional adverse reactions of enterobiasis and eosinophilia. Enterobiasis was reported in 1,8 % (5 patients) in the DUPIXENT groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with antihelminth treatment without DUPIXENT treatment discontinuation. Eosinophilia (blood eosinophils ≥ 3 000 cells/µL or deemed by the investigator to be an adverse event) was reported in 6,6 % of the DUPIXENT groups and 0,7 % in the placebo group.

The long-term safety of DUPIXENT was assessed in an open-label extension study (EXCURSION) in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in VOYAGE. Among 365 patients who entered EXCURSION, 350 completed 52 weeks of treatment and 228 patients completed a cumulative treatment duration of 104 weeks (VOYAGE and EXCURSION).

The safety profile of DUPIXENT in children with asthma 6 to 11 years of age who participated in the 52 weeks long-term safety study (EXCURSION) was consistent with the safety profile observed in the pivotal asthma study (VOYAGE) for 52 weeks of treatment.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

A total of 722 adult patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks duration (SINUS-24 and SINUS-52). The safety pool consisted of data from the first 24 weeks of treatment.

Table 6 summarises the adverse reactions that occurred at a rate of at least 1 % in patients treated with DUPIXENT and at a higher rate than in their respective comparator group in SINUS-24 and SINUS-52.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥ 10 %); common (≥ 1 % and < 10 %); uncommon (≥ 0,1 % and < 1 %); rare (≥ 0,01 % and < 0,1 %); very rare (< 0,01 %); not known (cannot be estimated from available data).

Table 6: Adverse reactions occurring in ≥ 1 % of the DUPIXENT group in SINUS-24 and SINUS-52 and greater than placebo (24-week safety pool)

MedDRA system organ class	Frequency	Adverse reaction
Infections and infestations	Common	Conjunctivitis
General disorders and administration site conditions	Common	Injection site reactions [a]

[a] Injection site reactions cluster includes injection site reactions and swelling.

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

PRURIGO NODULARIS

A total of 309 adult patients with prurigo nodularis (PN) were evaluated in two 24-week randomised, double-blind, placebo-controlled, multicentre trials (PRIME and PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both studies.

Table 7 summarises the adverse reactions that occurred at a rate of at least 1 % in patients treated with DUPIXENT and at a higher rate than in their respective comparator group in PRIME and PRIME2.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥ 10 %); common (≥ 1 % and < 10 %); uncommon (≥ 0,1 % and < 1 %); rare (≥ 0,01 % and < 0,1 %); very rare (< 0,01 %); not known (cannot be estimated from available data).

Table 7: Adverse reactions occurring in ≥ 1 % of the DUPIXENT group in PRIME and PRIME2 and greater than placebo (safety pool)

MedDRA system organ class	Frequency	Adverse reaction
Infections and infestations	Common	Conjunctivitis [a]

[a] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation. In the PN program, the observed events from the cluster in the DUPIXENT arm were conjunctivitis and allergic conjunctivitis.

Description of selected adverse reactions

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, angioedema and serum sickness or serum sickness-like reactions have been reported following the administration of DUPIXENT (section 4.4).

Conjunctivitis- and keratitis-related events

Conjunctivitis- and keratitis-related events occurred more frequently in atopic dermatitis patients who received DUPIXENT in the placebo-controlled atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period.

The respective rates of conjunctivitis and keratitis remained similar at 5 years in the long-term OLE study (AD-1225).

Among asthma patients the frequency of conjunctivitis and keratitis was low and similar between DUPIXENT and placebo.

In patients with CRSwNP and PN, the frequency of conjunctivitis was low, although the frequency in the DUPIXENT group was higher than in the placebo group.

There were no cases of keratitis in the CRSwNP and PN development programmes.

Eosinophils

DUPIXENT-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo in the atopic dermatitis, asthma and CRSwNP indications. Eosinophil counts declined to near baseline levels during study treatment. Eosinophil counts continued to decline below baseline during the open-label extension study in asthma patients.

Compared to placebo, no increase in mean blood eosinophil counts was observed in PN (PRIME and PRIME2).

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

Treatment-emergent eosinophilia (≥ 5 000 cells/µL) was reported in < 2 % of DUPIXENT treated patients and < 0,5 % in placebo-treated patients.

In PN the incidence of treatment-emergent eosinophilia (≥ 500 cells/µL) was lower in DUPIXENT than in the placebo group.

Treatment-emergent eosinophilia (≥ 5 000 cells/µL) was reported in 8,4 % of DUPIXENT treated patients and 0 % in placebo-treated patients in study AD-1539, with median eosinophil counts declining below baseline at end of treatment period.

Infections

In atopic dermatitis, asthma, CRSwNP and PN, the rate of serious infections was similar between DUPIXENT and placebo-treated patients.

No increase was observed in the overall incidence of infections or serious infections with DUPIXENT compared to placebo in the primary safety pool for atopic dermatitis clinical studies. In the 16-week monotherapy clinical studies primary safety pool, serious infections were reported in 0,5 % of patients treated with DUPIXENT and 1,0 % of patients treated with placebo. In the 52-week CHRONOS study, serious infections were reported in 0,2 % of patients treated with DUPIXENT and 0,6 % of patients treated with placebo. The rates of serious infections remained stable at 5 years in the long-term OLE study (AD-1225).

No increase was observed in the overall incidence of infections with DUPIXENT compared to placebo in the safety pool for asthma clinical studies. In the 24-week safety pool, serious infections were reported in 1,0 % of patients treated with DUPIXENT and 1,1 % of patients treated with placebo. In the 52-week QUEST study, serious infections were reported in 1,3 % of patients treated with DUPIXENT and 1,4 % of patients treated with placebo.

No increase was observed in the overall incidence of infections with DUPIXENT compared to placebo in the safety pool for CRSwNP clinical studies. In the 24-week safety pool, serious infections were reported in 0,7 % of patients treated with DUPIXENT and 1,1 % of patients treated with placebo. In the 52-week SINUS-52 study, serious infections were reported in 1,3 % of patients treated with DUPIXENT and 1,3 % of patients treated with placebo.

No increase was observed in the overall incidence of infections with DUPIXENT compared to placebo in the safety pool for PN clinical studies. In the safety pool, serious infections were reported in 1,3 % of patients treated with DUPIXENT and 1,3 % of patients treated with placebo.

Patients with existing active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, HIV and opportunistic infections such as progressive multifocal leukoencephalopathy (PML) were not studied in dupilumab clinical trials.

Immunogenicity

There is a potential for immunogenicity with dupilumab.

Approximately 5 % of patients with atopic dermatitis, asthma or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antidrug antibodies (ADA) to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralising antibodies. Similar results were observed in adult patients with PN who received DUPIXENT 300 mg Q2W for 24 weeks, paediatric patients (6 months to 11 years of age) with atopic dermatitis who received either DUPIXENT 200 mg Q2W, 200 mg Q4W or 300 mg Q4W and patients 6 to 11 years of age with asthma who received either DUPIXENT 100 mg Q2W or 200 mg Q2W up to 52 weeks.

Approximately 16 % of adolescent patients with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3 % exhibited persistent ADA responses, and approximately 5 % had neutralising antibodies.

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

Regardless of age or population, up to 4 % of patients in the placebo groups were positive for antibodies to DUPIXENT; up to 2 % exhibited persistent ADA responses and approximately 1 % had neutralising antibodies. ADA responses were not generally associated with impact on DUPIXENT exposure, safety or efficacy.

Less than 1 % of patients who received DUPIXENT at approved dosing regimens exhibited high titre ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (< 0,1 %), associated with high ADA titres (see section 4.4).

Post-marketing experience

The following additional adverse reactions have been reported during post-approval use of DUPIXENT. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).

Immune system disorders: angioedema.

Skin and subcutaneous tissue disorders: facial rash.

Musculoskeletal and connective tissue disorders: arthralgia.

Eye disorders: keratitis, ulcerative keratitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DUPIXENT is important. It allows continued monitoring of the benefit/risk balance of DUPIXENT. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email), https://ae.reporting.sanofi/ (web portal) or +27 11 256 3700 (tel), or
- SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

In clinical studies, no safety issues were identified with single intravenous doses up to 12 mg/kg.

Management

There is no specific treatment for DUPIXENT overdose.

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 13.12 Dermatological preparations – Others.

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids.

ATC Code: D11AH05.

5.1 Pharmacodynamic properties

Mechanism of action

Dupilumab is a human monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes.

IL-4 and IL-13 are key type 2 (including Th2) cytokines involved in atopic disease.

Type 2 inflammation plays an important role in the pathogenesis of multiple atopic conditions, including asthma, where it contributes to airflow limitation and increases risk of exacerbations. IL-4 and IL-13 act as major drivers of type 2 inflammation by activating multiple cell types (e.g. mast cells, lymphocytes, eosinophils, neutrophils, macrophages) and inducing multiple mediators (e.g.

IgE, histamine, eicosanoids, leukotrienes, chemokines and cytokines, including eotaxin/CCL11, TARC/CCL17 and IL-5) involved in type 2 inflammation. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of these markers of type 2 inflammation, including IgE, periostin, and multiple proinflammatory cytokines and chemokines (e.g. eotaxin, TARC), as well as fractional exhaled nitric oxide (FeNO), a marker of lung inflammation. Blocking the IL-4/IL-13 pathway with dupilumab in humanised animal models has been shown to prevent the downstream actions of these cytokines and chemokines, including goblet cell hyperplasia, airway smooth muscle hyperreactivity, eosinophilic lung inflammation, as well as other lung inflammatory processes, while also preventing lung function impairment; the decrease in eosinophilic lung inflammation occurs despite the presence of normal or increased blood eosinophil levels.

Dupilumab is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture.

Dupilumab has a molecular weight of approximately 147 kDa.

Pharmacodynamic properties

Atopic dermatitis

In clinical trials in atopic dermatitis patients, treatment with DUPIXENT was associated with decreases from baseline in concentrations of type 2-associated biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE and allergen-specific IgE in serum. A reduction of lactate dehydrogenase (LDH), a biomarker associated with AD disease activity and severity, was observed with DUPIXENT treatment.

DUPIXENT suppressed TARC relative to placebo as early as Week 2, with a trend of continued decline to a maximal and sustained suppression by Week 12. The majority of patients treated with DUPIXENT in the CHRONOS study (87,0 % and 84,9 % of patients in the DUPIXENT 300 mg Q2W and 300 mg QW, respectively) achieved normalised TARC levels compared to 20,0 % in the placebo group at Week 52.

Total IgE was reduced -74,8 % and -73,9 % by Week 52 (median change from baseline) with DUPIXENT 300 mg Q2W and 300 mg QW, respectively, compared to -0 % in the placebo group. Similar trends were observed for allergen specific IgEs. After 52 weeks of treatment, total IgE was normalised in 11,7 % and 15,9 % of patients receiving DUPIXENT 300 mg Q2W and 300 mg QW, respectively, compared to 4,4 % in the placebo group. Similar trends were observed with antigen-specific IgEs, including *S. aureus*-specific enterotoxin A, grass and tree allergens.

Asthma

Consistent with inhibition of IL-4 and IL-13 signalling, dupilumab treatment markedly decreased FeNO and circulating concentrations of eotaxin-3, total IgE, allergen-specific IgE, TARC and periostin in asthma subjects relative to placebo. These reductions in biomarkers of type 2 inflammation were comparable for the 200 mg Q2W and 300 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.

Chronic rhinosinusitis with nasal polyposis

Among CRSwNP subjects, urinary LTE4 (leukotriene E4), a marker associated with mast cell, basophil and eosinophil activation was also suppressed by dupilumab treatment.

5.2 Pharmacokinetic properties

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

Absorption

After a single subcutaneous (SC) dose of 75 – 600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3 – 7 days. The absolute bioavailability of dupilumab following a

SC dose is similar between AD, asthma, CRSwNP and PN patients, ranging from 61 % to 64 %, as determined by a population PK analysis.

Administration of a single loading dose of 600 mg on Day 1 leads to rapid attainment of clinically effective concentrations within 2 weeks.

For every other week dosing (Q2W) with either 200 mg or 300 mg, starting with a respective loading dose of 400 mg or 600 mg, or with 300 mg without a loading dose, population PK analysis determined steady state concentrations to be achieved by 16 weeks in a typical patient. Mean steady state trough concentration was 27 – 39 mg/L at 200 mg Q2W, 60 – 80 mg/L at 300 mg Q2W and 172 – 195 mg/L at 300 mg QW.

Dose linearity

Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentrationtime curve, increases with dose in a greater than proportional manner following single SC doses from 75 – 600 mg.

Distribution

A volume of distribution for dupilumab of approximately 4,6 L was estimated by population PK analysis, indicating that dupilumab is distributed primarily in the vascular system.

Biotransformation

Specific metabolism studies were not conducted because dupilumab is a protein. Dupilumab is expected to degrade to small peptides and individual amino acids.

Elimination

Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At therapeutic concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway.

After the last steady state dose of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W dupilumab, the median times to decrease below the lower limit of detection, determined by population PK analysis, ranged from 9 – 13 weeks in adults and adolescents and are approximately 1,5 times and 2,5 times longer in paediatric subjects 6 to 11 years of age and paediatric subjects less than 6 years of age, respectively.

Special populations

Gender

Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab as determined by population PK analysis.

Age

Age was not found to be associated with any clinically meaningful impact on the systemic exposure of DUPIXENT determined by population PK analysis in adults and in paediatric patients 6 to 17 years of age. In paediatric patients 6 months to 5 years of age, clearance increased with age but is accommodated in the recommended dose regimen.

Elderly patients

Of the 1 472 patients with atopic dermatitis exposed to DUPIXENT in a phase 2 doseranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger adult atopic dermatitis patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Of the 1 977 patients with asthma exposed to DUPIXENT, a total of 240 patients were 65 years or older. Efficacy and safety in this age group were similar to the overall study population. A total of 39 patients were 75 years or older.

Of the 440 patients with CRSwNP exposed to DUPIXENT, at total of 79 were 65 years and older. Efficacy and safety in this age group were similar to the overall study population. A total of 11 patients were 75 years and older.

Of the 152 patients with PN exposed to DUPIXENT, a total of 37 were 65 years of age or older. Efficacy and safety in this age group were similar to the overall study population. A total of 8 patients were 75 years of age or older.

Paediatric population

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), mean ± SD steady-state trough concentration was 54,5 ± 27,0 mg/L.

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 steadystate trough concentration was 86,0 ± 34,6 µg/mL and 98,7 ± 33,2 µg/mL, respectively.

For children 6 months to 5 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥ 15 to < 30 kg) or 200 mg (≥ 5 to < 15 kg), mean ± SD steady-state trough concentration was 110 ± 42,8 µg/mL and 109 ± 50,8 µg/mL, respectively.

The pharmacokinetics of dupilumab in paediatric patients (< 6 months of age) with atopic dermatitis have not been fully established.

Asthma

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in the QUEST study. The mean ± SD steady-state trough concentrations of dupilumab were 46,7 ± 26,9 µg/mL and 107 ± 51,6 µg/mL, respectively, for 200 mg or 300 mg administered every other week.

In the VOYAGE study, dupilumab pharmacokinetics was investigated in 405 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 µg/mL and 85,1 ± 44,9 µg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 to < 30 kg and ≥ 30 to < 60 kg resulted in predicted steady-state trough concentrations similar to the observed trough concentrations of 200 mg Q2W (≥ 30 kg) and 100 mg Q2W (< 30 kg), respectively. In addition, simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥ 15 to < 60 kg resulted in predicted steady-state trough concentrations similar to those demonstrated to be efficacious in adults and adolescents.

Pharmacokinetics in paediatric patients (< 6 years of age) with asthma have not been studied.

Chronic rhinosinusitis with nasal polyposis

CRSwNP does not normally occur in children. The pharmacokinetics of dupilumab has not been studied in children (< 18 years of age) with CRSwNP.

Prurigo nodularis

PN rarely occurs in children. The pharmacokinetics of dupilumab has not been studied in children (< 18 years of age) with PN.

Hepatic impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination.

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. No data are available in patients with severe renal impairment.

Body weight

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

For patients 6 to 17 years of age with atopic dermatitis, the recommended doses are 300 mg Q4W (15 kg to < 30 kg), 200 mg Q2W (30 kg to < 60 kg) and 300 mg Q2W (≥ 60 kg).

For patients 6 months to 5 years of age with atopic dermatitis, the recommended doses are 200 mg Q4W (5 kg to < 15 kg) and 300 mg Q4W (15 kg to < 30 kg).

For patients 6 to 11 years of age with asthma, the recommended doses are 300 mg Q4W (≥ 15 kg to < 30 kg), 200 mg Q2W or 300 mg Q4W (≥ 30 kg to < 60 kg) and 200 mg Q2W (≥ 60 kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DUPIXENT 200 mg pre-filled syringe with needle shield:

L-arginine hydrochloride (50 mM), L-histidine (20 mM), polysorbate 80 (0,2 % *m/v*), sodium acetate (12,5 mM), sucrose (5 % *m/v*) and water for injection, adjusted to pH 5,9 with acetic acid.

DUPIXENT 300 mg pre-filled syringe:

L-arginine hydrochloride (25 mM), L-histidine (20 mM), polysorbate 80 (0,2 % *m/v*), sodium acetate (12,5 mM), sucrose (5 % *m/v*) and water for injection, adjusted to pH 5,9 with acetic acid.

DUPIXENT 300 mg pre-filled syringe with needle shield:

L-arginine hydrochloride (25 mM), L-histidine (20 mM), polysorbate 80 (0,2 % *m/v*), sodium acetate (12,5 mM), sucrose (5 % *m/v*) and water for injection, adjusted to pH 5,9 with acetic acid.

6.2 Incompatibilities

In the absence of compatibility studies, DUPIXENT must not be mixed with other medicines.

6.3 Shelf life

DUPIXENT 200 mg: 36 months.

DUPIXENT 300 mg: 36 months.

6.4 Special precautions for storage

Store refrigerated at 2 °C to 8 °C in the original carton to protect from light.

If necessary, pre-filled syringes may be kept at room temperature up to 25 °C for a maximum of 14 days. Do not store above 25 °C. After removal from the refrigerator, the product must be used within 14 days or discarded.

Do not freeze.

Do not expose to heat.

Do not shake.

Do not use after the expiry date stated on the label and carton.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.5 Nature and contents of container

DUPIXENT 200 mg pre-filled syringe with needle shield:

DUPIXENT 200 mg pre-filled syringe with needle shield is provided as a single dose in a 1,14 mL siliconised clear Type I glass pre-filled syringe with a fixed 27-gauge 1,27 cm, thin wall stainless steel staked needle.

The pre-filled syringe is provided with a white polypropylene plunger rod, a white polycarbonate finger flange, and a safety system consisting of a polycarbonate needle guard with a stainless steel spring. The needle cap is not made with natural rubber latex.

Each pre-filled syringe is designed to deliver 200 mg of DUPIXENT 200 mg in 1,14 mL (175 mg/mL) solution.

Each cardboard box contains 1 or 2 pre-filled syringe/s.

Not all pack sizes may be marketed.

DUPIXENT 300 mg pre-filled syringe:

DUPIXENT 300 mg pre-filled syringe is provided as a single dose in a 2,25 mL siliconised clear Type I glass pre-filled syringe with a fixed 27-gauge 1,27 cm, thin wall stainless steel staked needle. The needle cap is not made with natural rubber latex.

Each pre-filled syringe is designed to deliver 300 mg of DUPIXENT 300 mg in 2 mL (150 mg/mL) solution.

Each cardboard box contains 1 or 2 pre-filled syringe/s.

Not all pack sizes may be marketed.

DUPIXENT 300 mg pre-filled syringe with needle shield:

DUPIXENT 300 mg pre-filled syringe with needle shield is provided as a single dose in a 2,25 mL siliconised clear Type I glass pre-filled syringe with a fixed 27-gauge 1,27 cm, thin wall stainless steel staked needle.

The pre-filled syringe is provided with a white polycarbonate plunger rod, a white polycarbonate finger flange, and a safety system consisting of a polycarbonate needle guard with a galvanised steel spring. The needle cap is not made with natural rubber latex.

Each pre-filled syringe is designed to deliver 300 mg of DUPIXENT 300 mg in 2 mL (150 mg/mL) solution.

Each cardboard box contains 1 or 2 pre-filled syringe/s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local

requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBERS

DUPIXENT 200 mg: 56/13.12/0056

DUPIXENT 300 mg: 51/13.12/0879

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

DUPIXENT 200 mg: 19 September 2023

DUPIXENT 300 mg: 26 January 2021

10. DATE OF REVISION OF THE TEXT

15 May 2025