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 prefilled 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 years and older with moderate-to-severe atopic dermatitis 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 adults and adolescents 12 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 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.

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)

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. 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 corticosteroids-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated.

Missed dose

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

Special populations

Paediatric patients

Atopic dermatitis

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

Asthma

Safety and efficacy in paediatric patients with asthma younger than 12 years have not been established (see section 5.2).

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.

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

Method of administration

Subcutaneous use.

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

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. 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 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. 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 asthma symptoms or acute exacerbations. 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 physician. 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 anti-helminth treatment, discontinue treatment with DUPIXENT until infection resolves.

Concomitant atopic conditions

Patients with atopic dermatitis who have comorbid 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.

Sucrose intolerance

Since DUPIXENT contains sucrose, patients with problems of sucrase-isomaltase intolerance

should not use DUPIXENT.

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 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 for use 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.

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 2526 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 with concomitant topical corticosteroids (TCS) was evaluated based on data from one randomised, double-blind, placebo-controlled, multicentre study. A total of 740 patients were treated up to 52 weeks.

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).

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.

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 the 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.

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, 6,1 % of the DUPIXENT 300 mg Q2W group.

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).

General disorders and administration site conditions

Very common: injection site erythema

Common: injection site oedema, injection site pruritus.

Description of selected adverse reactions

Hypersensitivity

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

Conjunctivitis and keratitis related events

Conjunctivitis and keratitis related events occurred more frequently in atopic dermatitis patients who received DUPIXENT. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period.
Among asthma patients the frequency of conjunctivitis and keratitis was low and similar between DUPIXENT and placebo.

Eosinophils

DUPIXENT-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. 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.

Across all 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.

Infections

In atopic dermatitis and asthma, 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 1,0 % of patients treated with placebo and 0,5 % of patients treated with DUPIXENT. In the 52-week CHRONOS study, serious infections were reported in 0,6 % of patients treated with placebo and 0,2 % of patients treated with DUPIXENT.

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.

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 6 % of patients with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed anti-drug antibodies (ADA) to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralising antibodies. Similar results were observed in paediatric patients (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 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, approximately 2 to 4 % of patients in the placebo groups were positive for antibodies to DUPIXENT; approximately 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 SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

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 signaling, 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.

5.2 Pharmacokinetic properties

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

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 and asthma patients, ranging from 61 % and 64 %, as determined by a population pharmacokinetic (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 after 16 weeks in a typical patient. Mean steady state trough concentration was 39 mg/L at 200 mg Q2W and 70 – 80 mg/L at 300 mg Q2W.

For weekly dosing (QW) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 13 weeks in a typical patient. Mean steady state trough concentration was 189 mg/L.

Dose linearity

Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time 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, the median time for dupilumab concentrations to decrease below the lower limit of detection, determined by population PK analysis, was 9 weeks for the 200 mg Q2W, 10 – 12 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Special populations

Elderly patients

The number of patients aged 65 and over in clinical studies was not sufficient to determine whether they respond differently from younger patients.

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

Paediatric patients

Atopic dermatitis

The safety and efficacy of dupilumab have been established in paediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis. Use of dupilumab in this age group is supported by study AD-1526, which included 251 adolescents aged 12 to 17 years old with moderate-to-severe atopic dermatitis and study AD-1652, which included 367 paediatric patients aged 6 to 11 years old with severe atopic dermatitis. Use is supported by study AD-1434, which enrolled patients who had completed study AD-1526 (136 moderate and 64 severe at the time of enrolment in study AD-1434) and patients who had completed study AD-1652 (110 moderate and 72 severe at the time of enrolment in study AD-1434). The safety and efficacy were generally consistent between paediatric, adolescent, and adult patients. Safety and efficacy in paediatric patients (< 6 years of age) with atopic dermatitis have not been established.

For adolescents 12 to 17 years of age patients 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 steady-state trough concentration was 86,0 ± 34,6 µg/mL and 98,7 ± 33,2 µg/mL, respectively.

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

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in QUEST study and received either 200 mg (N = 21) or 300 mg (N = 18) dupilumab (or matching placebo either 200 mg [N = 34] or 300 mg [N = 34]) every other week. Efficacy with respect to asthma exacerbations and lung function was observed in both adolescents and adults. For both the 200 mg and 300 mg every other week doses, significant 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 every other week dose, patients had a reduction in the rate of severe exacerbations that was consistent with that in adults. The adverse event profile in adolescents was generally similar to the adults (see section 4.8).

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.

The long-term safety and efficacy of dupilumab was assessed in 89 adolescent patients who were enrolled in an open-label extension study in moderate-to-severe asthma (TRAVERSE). In this study, patients were followed for up to 96 weeks, resulting in 99 patient-years cumulative exposure to dupilumab. The safety profile of dupilumab in TRAVERSE was consistent with the safety profile observed in asthma pivotal studies for up to 52 weeks of treatment. No additional adverse reactions were identified. In this study, the clinical benefit of dupilumab, including reduction in

exacerbations and improvement in lung function observed in pivotal asthma studies, was sustained up to 96 weeks.

Safety and efficacy in paediatric patients (< 12 years of age) with asthma have not been studied.

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 to 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.

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

Keep out of sight and reach of children.

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, a grey bromobutyl elastomeric plunger stopper and grey styrene-butadiene elastomeric needle shield with a transparent rigid polypropylene cap.

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 elastomeric needle cap (shield) 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.

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, a grey bromobutyl elastomeric plunger stopper and a grey styrene-butadiene elastomeric needle shield with or without a transparent rigid polypropylene cap. The elastomeric needle cap (shield) 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.

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 the pre-filled syringe, 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

elastomeric needle cap (shield) 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.

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

19 September 2023