Professional Information for DUPIXENT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUPIXENT® solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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 treatment of adult patients 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.

4.2 Posology and method of administration

Posology

DUPIXENT is administered by subcutaneous injection.

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.

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

Paediatric patients

Safety and efficacy in paediatric patients 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).

Method of administration

For the initial 600 mg dose, administer two 300 mg DUPIXENT injections subcutaneously at two different injection sites.

DUPIXENT is intended for use under the guidance of a healthcare 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.

4.3 Contraindications

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients (see section 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. 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 healthcare 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).

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

Safety and efficacy have not been established in allergic or atopic conditions other than atopic dermatitis. Patients with comorbid atopic conditions (such as asthma) should be advised not to adjust their treatment without consultation with their medical practitioner. When discontinuing DUPIXENT consider the potential effects on the 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.

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.

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

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 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).

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

Infections and infestations

Common: conjunctivitis, oral herpes, bacterial conjunctivitis, herpes simplex

Description of selected side effects

Hypersensitivity

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

Laboratory abnormalities

In clinical studies, transient eosinophilia was reported in < 2 % of patients treated with DUPIXENT.

Conjunctivitis and keratitis related events

Conjunctivitis and keratitis related events occurred in patients who received DUPIXENT. Most patients

with conjunctivitis or keratitis recovered or were recovering during the treatment period. The respective rates of conjunctivitis and keratitis remained similar at 3 years in the long-term OLE study (AD-1225).

Infections

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. The rates of serious infections remained stable at 3 years in the long-term OLE study (AD-1225).

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.

In a 52-week study, approximately 3 % of patients in the placebo group and 2 % of patients in the DUPIXENT group had anti-drug antibody (ADA) responses lasting more than 12 weeks. Among these patients, 0,7 % on placebo and 0,2 % treated with DUPIXENT also had neutralising antibody responses, which were not generally associated with loss of efficacy.

Patients positive for antibodies to dupilumab tended to have lower efficacy, however positivity does not preclude a clinical response. ADA responses were not generally associated with impact on DUPIXENT exposure, safety or efficacy. In the overall exposure pool, less than 0,1 % of patients 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) or 011 256 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

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.

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

Dupilumab has a molecular weight of approximately 147 kDa.

Pharmacodynamic effects

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.

5.2 Pharmacokinetic properties

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 estimated to be 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 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 10 weeks in a typical patient. Mean steady state trough concentration was 74 mg/L.

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.

Metabolism

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 10 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

The pharmacokinetics of dupilumab in paediatric patients 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DUPIXENT 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 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

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 pre-filled syringe:

DUPIXENT 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 in 2 mL (150 mg/mL) solution.

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

DUPIXENT pre-filled syringe with needle shield:

DUPIXENT 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 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

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

51/13.12/0879

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 January 2021

10. DATE OF REVISION OF THE TEXT

13 December 2021