Summary of the Risk Management Plan (RMP) for DUPIXENT®

DUPIXENT® (dupilumab)
Marketing Autorisation Holder : sanofi-aventis (suisse) sa
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Dupixent® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Dupixent® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of Dupixentt®.

1. THE MEDICINE AND WHAT IT IS USED FOR

DUPIXENT is authorized for:

Atopic dermatitis:

DUPIXENT is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy.

Asthma:

DUPIXENT is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment. See SmPC for the full indication.

It contains dupilumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of DUPIXENT's benefits can be found in DUPIXENT's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of DUPIXENT, together with measures to minimize such risks and the proposed studies for learning more about DUPIXENT's risks, are outlined in the next sections.

Measures to minimize the risks identified for DUPIXENT:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.
- Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) so that immediate action can

be taken as necessary. These measures constitute routine pharmacovigilance activities.

2.1. List of important risks and missing information

Important risks of DUPIXENT are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DUPIXENT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 1 - List of important risks and missing information

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	Malignancy
Missing information	Use in pediatric AD patients <18 years of age and asthma patients <12 years of age Use in pregnant and lactating women Conjunctivitis related events in AD patients Long-term safety

AD: Atopic dermatitis

2.2. Summary of important risks

Table 2 – Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)

Important identified risk: Systemic hypersensitivity (including events associated with	
Evidence for linking the risk to the medicine	Clinical trial data and literature.
Risk factors and risk groups	All patients are at risk of developing systemic hypersensitivity reactions. Risk factors for serum sickness include patient age, dose, duration and the heterologous protein involved in medication. Serum sickness-like reactions are more common in children. Intermittent exposure to a heterologous protein is associated with higher rates of serum sickness-like reactions compared with continuous exposure. (1)(2) Risk factors for anaphylaxis include known hypersensitivity to dupilumab or the excipients in the formulation.

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine Additional risk minimization measures: None

PIL: Patient Infomration Leaflet; SmPC: Summary of Product Characteristics.

Table 3 – Important potential risk: Malignancy

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	None
Risk factors and risk groups	Risk depends on age, genetics, and exposure to risk factors which include smoking, insufficient physical activity, alcohol, diet, overweight and obesity, and infections. (3).
Risk minimization measures	Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Prospective cohort study of Dupixent® (dupilumab) safety in long-term use in adult atopic dermatitis patients in Europe, with a targeted follow-up of 5 years Short study name Study OBS15906

Table 4 - Missing information: Use in pediatric AD patients <18 years of age and asthma patients <12 years of age

Missing information: Use in pediatric AD patients <18 years of age and asthma patients <12 years of age	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2 and 5.2 PIL section 2 Prescription only medicine Additional risk minimization measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pediatric PK studies R668-AD-1434, R668-AD-1526 (adolescent confirmatory trial), R668-AD-1539 and R668-AD-1652, EFC14153, EFC14771, LTS14424.

AD: Atopic Dermatitis; PIL: Patient Information Leaflet; PK: Pharmacokinetics; SmPC: Summary of Product Characteristics.

Table 5 - Missing information: Use in pregnant and lactating women

Missing information: Use in pregnant and lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: Pregnancy registry study (R668-AD-1639) in asthma and AD patients Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients

AD: Atopic Dermatitis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 6 - Missing information: Conjunctivitis related events in AD patients

Missing information: Conjunctivitis related events in AD patients	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: Ophthalmology substudy in R668-AD-1225

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 7 - Missing information: Long-term safety

Missing information: Long-term safety	
Risk minimization measures	Prescription only medicine
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: Prospective cohort study of Dupixent® (dupilumab) safety in long-term use in adult atopic dermatitis patients in Europe, with a targeted follow-up of 5 years Short study name Study OBS15906

2.3. Post-authorisation development plan

2.3.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of DUPIXENT.

2.3.2 Other studies in post-authorisation development plan

Table 8 - Other studies in post-authorization development plan

Pregnancy registry (R668-AD-1639) (Cat. 3)

Purpose of the study:

To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes in asthma and AD patients.

Once the asthma indication is approved in the US, the study will be amended to include separate exposed and unexposed cohorts of women with asthma. Although there is no specific concern surrounding differential risks of dupilumab exposure for pregnant women with asthma from the clinical trials, the effect of dupilumab on pregnancy outcomes for women with asthma is still considered missing information. Further, the risk of adverse pregnancy outcomes is known to be greater for women with asthma from the general population than for other populations of women. Therefore, it is considered to be of importance to study these outcomes separately to better identify risks that may be associated with dupilumab exposure and asthma.

Pregnancy Outcomes Database Study (R668-AD-1760) (Cat. 3)

Purpose of the study:

To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy and compare these to each of the two comparator cohorts of pregnant women with AD; one exposed to other systemic medications or phototherapy used for the treatment of AD (never exposed to dupilumab) and the other comprised of women who were not exposed to these treatments during pregnancy

A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041) (Cat. 3)

Purpose of the study:

To assess the long term safety, efficacy, PK, and immunogenicity of REGN668 in patients with moderate-to-severe AD.

A randomized, double blind, placebo controlled study to investigate the efficacy and safety of dupilumab in patients 12 to <18 years of age, with moderate to severe AD Phase III) (EFC1526) (R668-AD-1526) (Cat. 3)

Purpose of the study:

To demonstrate the efficacy of dupilumab in patients ≥12 years to <18 years of age with moderate-to-severe AD.

A phase 2/3, randomized double-blind study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 months to <6 years with severe atopic dermatitis (R668-AD-1539) (Cat. 3)

Purpose of the study:

To characterize the safety and PK of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age; demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS.

A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients, ≥6 years to <12 years of age, with severe atopic dermatitis (Phase III) (R668-AD-1652) (Cat. 3)

Purpose of the study:

To demonstrate the safety and efficacy of dupilumab administered concomitantly with TCS in patients, ≥6 years to <12 years of age, with severe AD..

An single arm extension study to assess the long term safety of dupilumab in patients 6 to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) (Cat. 3)

Purpose of the study:

To assess the long term safety of dupilumab in pediatric patients with AD.

Prospective cohort study of Dupixent® (dupilumab) safety in long-term use in adult atopic dermatitis patients in Europe (OBS15906) (Cat. 3)

Purpose of the study:

To monitor for long-term adverse events, in particular malignancy, with a targeted follow-up of 5 years.

Pediatric asthma study in children 6 to <12 years of age who have uncontrolled persistent asthma (EFC14153) (Cat. 3)

Purpose of the study:

To assess the efficacy and safety of dupilumab in children 6 to less than 12 years old with uncontrolled persistent asthma.

Pediatric asthma study in children 6 months to <6 years of age with recurrent severe asthmatic wheezing uncontrolled by ICS (EFC14771) (Cat. 3)

Purpose of the study:

To assess the efficacy and safety of dupilumab in children 6 months to less than 6 years old with recurrent severe asthmatic wheezing uncontrolled by ICS.

Long term safety and tolerability study of dupilumab in children 6 months to <12 years of age who participated in previous dupilumab asthma clinical studies (LTS14424) (Cat. 3)
Purpose of the study: To evaluate the long-term safety and tolerability of dupilumab in children 6 months to less than 2 years patients who participated in previous dupilumab asthma clinical studies.

AD: Atopic Dermatitis; ICS: Inhaled Corticosteroid; PK: Pharmacokinetics; TCS: Topical Corticosteroid; US: United States.