Summary of risk management plan for DUPIXENT (Dupilumab)

This is a summary of the RMP for DUPIXENT. The RMP details important risks of DUPIXENT, how these risks can be minimized, and how more information will be obtained about DUPIXENT's risks and uncertainties (missing information).

DUPIXENT's SmPC and its package leaflet give essential information to healthcare professionals and patients on how DUPIXENT should be used.

This summary of the RMP for DUPIXENT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DUPIXENT's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

DUPIXENT is authorized for:

Atopic dermatitis

Adults and adolescents

DUPIXENT is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age

DUPIXENT is indicated for the treatment of severe AD in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents

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), see section 5.1, who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age

DUPIXENT is indicated in children 6 to 11 years old 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), see section 5.1, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis

DUPIXENT is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids (SCSs) and/or surgery do not provide adequate disease control.

Prurigo Nodularis (PN):

DUPIXENT is indicated for the treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy.

Eosinophilic Esophagitis (EoE):

DUPIXENT is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1).

See SmPC for the full indication.

It contains dupilumab as the active substance and it is given by subcutaneous (SC) 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

II. 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 medicinal products can be:

- 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.

If important information that may affect the safe use of DUPIXENT is not yet available, it is listed under "missing information" outlined in the next section.

II.A. 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) Conjunctivitis and keratitis related events in AD patients
Important potential risk	None
Missing information	Use in pregnant and lactating women Long-term safety in adult and paediatric patients

AD: Atopic Dermatitis.

II.B. Summary of important risks

Table 2 - Important identified risk with corresponding risk minimization activities: Systemic hypersensitivity (including events associated with immunogenicity)

Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)	
Evidence for linking the risk to the medicine	Clinical trial data, literature and postmarketing pharmacovigilance.
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. [a, b] 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

a Black RE, Gunn RA. Hypersensitivity reactions associated with botulinal antitoxin. Am J Med. 1980 Oct;69(4):567-70. doi: 10.1016/0002-9343(80)90469-6.

b Kugathasan S, Levy MB, Saeian K, Vasilopoulos S, Kim JR, Prajapati O, et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. Am J Gastroenterol. 2002 Jun;97(6):1408-14. doi: 10.1111/j.1572-0241.2002.05784.x.

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

Table 3 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Conjunctivitis and keratitis related events in AD patients

Important identified risk: Conjunctivitis and keratitis related events in AD patients	
Evidence for linking the risk to the medicine	Conjunctivitis and keratitis related events have been reported in dupilumab clinical trials, the postmarketing setting and the literature, predominantly in AD patients.

Important identified risk: Conjunctivitis and keratitis related events in AD patients	
	Conjunctivitis and keratitis related events are considered ADRs for dupilumab (SmPC section 4.8 and Package Leaflet section 4).
Risk factors and risk groups	Conjunctivitis: As per Triester AD et al, severe conjunctivitis was more likely to develop in patients with more severe baseline AD and an increased atopic phenotype. [a] Akinlade B et al, stated that among AD patients, the increased incidence of conjunctivitis was associated with higher AD severity at baseline and prior history of conjunctivitis. [b] Keratitis/ulcerative keratitis: A review of the literature found a list of risk factors for keratitis. Chief amongst these are: autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosous and inflammatory bowel disease, [c, d] contact lenses; [e] herpes simplex and zoster infections; [f, g] and severity of AD. [h] Autoimmune conditions are overrepresented in the AD population and thus present an important risk factor for keratitis [i, j, k] Patients with AD are susceptible to eczema herpeticum, which is caused by extensive infection of the skin by herpes virus. This can lead to keratoconjunctivitis. [l] Lin TY et al stated that risk factors for development of microbial keratitis include contact lens wear as the most common predisposing factors, followed by ocular and systemic diseases, trauma and ocular surgery. [m]
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 sub-study in LTS14041 (R668-AD-1225)

a Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. JAMA Dermatol. 2018 Oct 1;154(10):1208-11. doi: 10.1001/jamadermatol.2018.2690.

b Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019 Sep;181(3):459-73. doi: 10.1111/bjd.17869.

c Patel SJ, Lundy DC. Ocular manifestations of autoimmune disease. Am Fam Physician. 2002 Sep 15;66(6):991-8.

d Mady R, Grover W, Butrus S. Ocular complications of inflammatory bowel disease. ScientificWorldJournal. 2015;2015(438402):1-5. doi: 10.1155/2015/438402.

e Collier SA, Gronostaj MP, MacGurn AK, Cope JR, Awsumb KL, Yoder JS, et al. Estimated burden of keratitis--United States, 2010. MMWR Morb Mortal Wkly Rep. 2014 Nov 14;63(45):1027-30.

f Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: an epidemiologic update. Surv Ophthalmol. 2012 Sep;57(5):448-62. doi: 10.1016/j.survophthal.2012.01.005.

g Shaikh S, Ta CN. Evaluation and management of herpes zoster ophthalmicus. Am Fam Physician. 2002 Nov 1;66(9):1723-30.

h Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Acad Dermatol. 2017 Aug;77(2):280-6.e1. doi: 10.1016/j.jaad.2017.03.003.

i Andersen YM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Autoimmune diseases in adults with atopic dermatitis. J Am Acad Dermatol. 2017 Feb;76(2):274-80.e1.

j Narla S, Silverberg JI. Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study. J Am Acad Dermatol. 2019 Feb;80(2):382-9. doi: 10.1016/j.jaad.2018.09.025.

k Schmitt J, Schwarz K, Baurecht H, Hotze M, Folster-Holst R, Rodriguez E, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol. 2016 Jan;137(1):130-6. doi: 10.1016/j.jaci.2015.06.029.

l Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. J Allergy Clin Immunol. 2009 Aug;124(2):260-9, 269.e1-7. doi: 10.1016/j.jaci.2009.05.020.

m Lin TY, Yeh LK, Ma DH, Chen PY, Lin HC, Sun CC, et al. Risk Factors and Microbiological Features of Patients Hospitalized for Microbial Keratitis: A 10-Year Study in a Referral Center in Taiwan. Medicine (Baltimore). 2015 Oct;94(43):e1905. doi: 10.1097/MD.0000000000001905.

AD: Atopic Dermatitis; ADR: Adverse Drug Reaction; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 4 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: 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), Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients

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

Table 5 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety in adult and paediatric patients

Missing information: Long-term safety	
Risk minimization measures	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Studies LTS14041 (R668-AD-1225), LTS1434 (R668-AD-1434), LTS14424, and PEDISTAD registry-based study (study code pending protocol development)

II.C. Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

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

II.C.2 Other studies in post-authorization development plan

Table 6 - 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. The study initially included exposed and unexposed cohorts of women with moderate-to-severe AD. The study was 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. Data from other indications (including CRSwNP, EoE, and PN) will be collected in the “exposure series.

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 adult patients with moderate-to-severe AD.

An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months 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.

An open-label study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Phase III) (LTS14424) (Cat. 3)

Purpose of the study:

To assess the long-term safety, tolerability and efficacy of dupilumab in pediatric patients with asthma.

A registry-based study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis (AD) (Cat. 3)

Purpose of the study:

- To describe the baseline clinical and demographic characteristics of pediatric patients with moderate-to-severe AD.
- To evaluate the long-term safety of dupilumab in patients with moderate-to-severe AD aged ≥6 months to <6 years.

AD: Atopic Dermatitis; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; PK: Pharmacokinetic; PN: Prurigo Nodularis.