Taiwan Food and Drug Administration

Assessment Report

Trade Name：杜避炎注射劑 300 毫克 /
Dupixent solution for injection 300 mg

Active Ingredient：Dupilumab

License Number： 衛部菌疫輸字第 001082 號

Applicant：賽諾菲股份有限公司

Approval Date： 107/05/10

Indication：
Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

DUPIXENT 可用於治療中度至重度異位性皮膚炎且對局部處方治療控制不佳或不適合使用該療法的成人病人。
DUPIXENT 可併用或不併用局部皮質類固醇治療。

1. Background Information

Trade Name	杜避炎注射劑 300 毫克/ Dupixent solution for injection 300 mg
Active Ingredient(s)	Dupilumab
Applicant	賽諾菲股份有限公司
Dosage Form & Strengths	Injection 300 mg
Indication	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
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. Dupixent can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.
Pharmacological Category **ATC Code**	A16AB17

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Dupilumab, the brand name Dupixent®, is a recombinant fully human IgG4 monoclonal antibody that binds specifically to the alpha sub-unit of the Type I and II interleukin-4 receptors (IL- 4Rα). Therefore dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). The manufacturer of dupilumab drug substance (DS) and formulated drug substance (FDS) is Regeneron Pharmaceuticals, Inc. located in Rensselaer, USA.

Dupilumab produced in CHO cells has a predicted protein molecular weight of 146,897.0 Da

and contains a single, conserved N-glycosylation site (Asn302) in the Fc region of each heavy chain. Each dupilumab heavy chain contains 452 amino acids and each light chain contains 219 amino acids. Dupilumab heavy chains contain a serine to proline mutation at amino acid in the hinge region to stabilize the interaction between heavy chains. Detailed description of the origin, history and preparations of cell banks including MCBs, WCBs and EOPs were provided. Adventitious and endogenous agent safety testing, identity and genetic stability for cell banks were conducted based on the recommendations in ICH guidance. Raw materials of direct and indirect biological origin are justified. Characterization studies were presented including primary and high order structure, glycosylation, disulfide structure, charge and size heterogeneity, binding ability and biological activity analyzed by cell-based assays, as well as product-related and process-related impurities. Rationale for not routine testing some process-related impurities was provided based on in-process testing data, assessment of worst case scenario and permitted daily exposure levels. Manufacturing process and in-process controls, manufacturing process development histories for total 4 processes, comparability studies, impurity profiles, process validation, specification, analytical methods and validations, batch analyses, reference materials and virus clearance studies, were provided abundantly to demonstrate the quality and consistency of dupilumab DS and FDS using commercial process.

Long-term (-30 ± 10℃) and accelerated stability studies have been carried out for dupilumab DS and FDS primary and supporting batches and the results are provided. The long-time stability is based on DS batches and FDS batches produced with the commercial process and composition. To complete the long-term stability studies of the primary and supporting DS and FDS batches are committed by the applicant, as well as for annual lots.

2.1.2 Drug product

The drug product proposed for marketing is a clear to slightly opalescent, colorless to pale yellow, aqueous buffered, pH 5.9 sterile solution containing 2 mL of 150 mg/mL dupilumab for subcutaneous (SC) injection. Two presentations are supplied including single-use prefilled syringe (PFS) and PFS with safety system (PFS-S). A primary container referred to as a “bulk prefilled syringe (bulk PFS)” is used to be comprised of PFS and PFS-S. Sanofi Winthrop Industrie in France is the manufacturer for both PFS and PFS-S. Cook Pharmica LLC in USA is the manufacturer for PFS only.

The compositions are listed and the excipients for FDS and DP are complied with Ph. Eur., USP, NF or JP. No novel excipients or animal/human origins are used in the formulation. DP manufacturing process and formulation development were described. The container closure system has been shown to comply with the essential requirements of medical devices in EU and FDA and the relevant ISO requirements. Assessments for abilities of protection, safety

and compatibility including container closure integrity testing, extractables and leachables for the container closure system were presented. Manufacturing process/in process controls, process validation, specification and batch analyses were provided and show that the manufactures of PFS and PFS-S are controlled properly and consistently.

The release specification and shelf life specification for product bulk PFS, PFS and PFS-S include appearance, general solution properties, identity, purity/impurity, potency by cell-based bioassay, quantity, adventitious agents and syringe with/without safety system performance properties. The specifications of bulk PFS, PFS and PFS-S are generally acceptable.

Stability studies were conducted under long-term (5 ± 3℃), accelerated and stress conditions for bulk PFS, PFS and PFS-S. The photostability studies for PFS and PFS-S were performed and showed that exposure to light should be limited. The currently available data of long-term stability studies for buck PFS, PFS and PFS-S has shown stable results for 6 months at 5 ± 3℃, protected from light. Therefore, the product shelf life of 6 months at 5 ± 3℃ for PFS and PFS-S is acceptable.

In conclusion, information on the drug substance and finished drug product is regarded as adequate to support the quality of the application.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Dupilumab is a fully human monoclonal antibody directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, which is a component of interleukin-4 (IL-4) receptors Type I and Type II, that mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). Dupilumab binds human IL-4Rα with high affinity. *In vitro* and *in vivo* studies demonstrated the ability of dupilumab to antagonize IL-4 (Type I and Type II) and/or IL-13 (Type II) receptor signaling. Dupilumab is expected to inhibit the Th2 pathway selectively, which is responsible for several pathophysiological mechanisms.

2.2.2 Toxicological Studies

Since dupilumab does not cross-react with the general toxicological species, homologous antibodies, REGN646 and REGN1103, which are respectively specific for cynomolgus monkey and mouse IL-4Rα, were developed and used to evaluate the nonclinical safety of IL-4Rα blockade. No REGN646 related adverse effects (including effects on the immune system) were observed in these repeat dose toxicology studies in cynomolgus monkeys up to 100 mg/kg/week, the highest dose tested. No target organs of toxicity were identified in these studies. The NOAEL following weekly REGN646 administration to cynomolgus monkeys

for 6 months was 100 mg/kg/week by the subcutaneous route and 25 mg/kg/week by intravenous infusion. No genetic toxicology or carcinogenicity studies have been conducted with dupilumab. Instead, a weight-of-evidence assessment of carcinogenic potential of dupilumab was conducted and concluded that chronic administration of dupilumab poses no increased risk of cancer. Furthermore, no REGN1103- or REGN646-related adverse effects were observed in segment I mouse study and enhanced PPND monkey study, respectively.

In conclusion, the provided non-clinical data of dupilumab itself or homologous antibodies is adequate. The associated information for the nonclinical pharmacology, toxicology and pregnancy in the proposed label are also acceptable.

2.3 Clinical Pharmacology Evaluation

Dupilumab was well absorbed following sc injection with absolute BA of 64% based on POP PK analysis. It exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. Following SC administration, a fully saturated beta phase was observed in sc 300 mg dose group. The accumulation factor based on C_{trough} is about 1.4-folds and 2-folds from week 2 to week 16 reaching about 75 μg/mL and 183 μg/mL for 300 mg q2w and 300 mg qw, respectively. Co-administration of topical corticosteroid did not affect dupilumab PK. During development, the comparability of the change in cell line, manufacturing process, formulations and presentations has been demonstrated and acceptable.

Dupilumab is largely distributed in the vascular compartment with a small volume of distribution (4.6 L). No metabolism/excretion studies were performed for dupilumab. At higher concentrations, dupilumab elimination is primarily through a non-saturable, linear proteolytic pathway, while at lower concentrations, the nonlinear saturable IL-4Rα target-mediated elimination predominates. After the last steady-state dose of 300 mg Q2W or 300 mg QW dupilumab, the median time to non-detectable concentration (<78 ng/mL) are 10 and 13 weeks, respectively.

In population PK analysis, weight, ADA, albumin, race, and baseline EASI score were statistically significant covariates. However, none of them indicated a need for dose adjustment. No dose adjustment was also recommended for elderly population. No formal trial for evaluation hepatic or renal impairment on the dupilumab PK was conducted. According to the updated in vivo DDI study, it indicated dupilumab has no significant impact on the PK of CYP3A4, CYP2C19, CYP2C9, CYP1A2 or CYP2D6 substrate. Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of 3 pivotal, randomized, double-blind, placebo-controlled clinical studies of similar design were provided to demonstrate the efficacy of dupilumab. Two studies (R668-AD-1334 [SOLO 1], R668-AD-1416 [SOLO 2]) demonstrated the efficacy of dupilumab monotherapy in adults (≥18 years) with moderate-to-severe atopic dermatitis (AD) whose disease was not adequately controlled with topical medications or for whom topical treatment was medically inadvisable. One study (R668-AD-1224 [CHRONOS]) demonstrated the efficacy of dupilumab administered concomitantly with topical corticosteroid (TCS) in in adults (≥18 years) with moderate-to-severe atopic dermatitis (AD) that was not adequately controlled with medium to high potency TCS (± topical calcineurin inhibitors (TCI), as appropriate).

The co-primary endpoints, the proportion of patients with Investigator's Global assessment (IGA) 0 or 1 and a reduction from baseline of ≥2 points at Week 16 and the proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 16, were statistically significantly higher in the dupilumab 300 mg Q2W and dupilumab 300 mg QW groups than the placebo group (p-value <0.0001) in all 3 studies.

Table below summarizes the response rates of the 3 studies per treatment group in the FAS.

Co-Primary Endpoints		**Placebo**	**Dupilumab 600 mg loading dose**	
			300 mg Q2W	**300 mg QW**
IGA 0 or 1 & reduction from baseline ≥2 points at Week 16, n (%)	**Study [SOLO 1]**	(N=224) 23 (10.3)	(N=224) 85 (37.9)	(N=223) 83 (37.2)
	Study [SOLO 2]	(N=236) 20 (8.5)	(N=233) 84 (36.1)	(N=239) 87 (36.4)
		Placebo + TCS	**300 mg Q2W + TCS**	**300 mg QW + TCS**
	Study [CHRONOS]	(N=315) 39 (12.4)	(N=106) 41 (38.7)	(N=319) 125 (39.2)
EASI-75 at Week 16, n (%)	**Study [SOLO 1]**	(N=224) 33 (14.7)	(N=224) 115 (51.3)	(N=223) 117 (52.5)
	Study [SOLO 2]	(N=236) 28 (11.9)	(N=233) 103 (44.2)	(N=239) 115 (48.1)
		Placebo + TCS	**300 mg Q2W + TCS**	**300 mg QW + TCS**
	Study [CHRONOS]	(N=315) 73 (23.2)	(N=106) 73 (68.9)	(N=319) 204 (63.9)

2.4.2 Safety Results

739 subjects with atopic dermatitis were treated with dupilumab for at least 1 year (645

patients with 300 mg weekly and 58 patients with 300 mg every 2 weeks).

The most common adverse reactions in subjects treated with dupilumab were injection site reactions, conjunctivitis and oral herpes. In monotherapy trials through week 16, oral herpes was reported in 3.8 % of dupilumab 300 mg Q2W group, 2.5% of dupilumab 300 mg QW group and 1.5% of placebo group.

Hypersensitivity
In clinical trials, two subjects experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab.
Conjunctivitis
In monotherapy trials through week 16, the rate of conjunctivitis was 9.3% in the dupilumab 300 Q2W group, 7.9% in the dupilumab 300 mg QW group and 2.1% in the placebo group. During the 52-week treatment period of concomitant topical corticosteroid trial, treatment emergent conjunctivitis was reported in 13.6% of the dupilumab 300 mg Q2W group, 19.4% of dupilumab 300 mg QD group and in 7.9% of the placebo group.
Injection site reaction
Injection site reaction was reported in 9.6 % of dupilumab 300 mg Q2W group, 13.9% of dupilumab 300 mg QW group and 5.4% of placebo group.
Immunogenicity
In 52-week concomitant topical corticosteroid trial, treatment-emergent anti-drug antibody positive responses were observed in 6.6% of the placebo group, 5.7% of the dupilumab 300 mg Q2W group and 4.5% of the dupilumab 300 mg QW group.

2.5 Bridging Study Evaluation

Sponsor has submitted one Japanese single dose PK study, one population PK analysis in which 17% of target patients were Asian following therapeutic dosing regimen, and a PD comparison between Asians and Non-Asians. No significant ethnic difference was observed. A phase 3 study (SOLO-2) included 708 subjects of whom 85 subjects were from Asian countries (28 in the dupilumab 300 mg Q2W group, 29 in the dupilumab 300 mg QD group and 28 in the placebo group).

In Asian population, the proportion of patients who achieved IGA 0 or 1 and a reduction from baseline of ≥2 points at week 16 was 32.1% in the dupilumab 300 mg Q2W, 31.0% in the dupilumab 300 mg QD group and 0% in the placebo group. The efficacy results and safety profiles in Asian population were similar to those observed in overall population.
Therefore, bridging study of dupilumab was waived.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Three adequate and well-controlled studies were provided to demonstrate the efficacy of dupilumab for the treatment of patients with moderate to severe AD. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.

3. Post-Marketing Requirements

Routine pharmacovigilance should be performed.