NATIONAL PHARMACEUTICAL REGULATORY DIVISION MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
Dupixent 300 mg Solution for Injection in Pre-filled Syringe (201804060299A) (MAL19056001AZ)

ACTIVE INGREDIENT:
Dupilumab 150 mg/ml

PRODUCT REGISTRATION HOLDER:
Sanofi-Aventis (Malaysia) Sdn. Bhd.

PRODUCT MANUFACTURER:
Sanofi Winthrop Industrie, 1051 Boulevard Industriel, 76580 Le Trait, France

APPROVAL DATE:
2 May 2019 (DCA 334)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

Dupixent is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescriptions therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.

1.2 Approved 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.

If a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patients to wait until the next dose on the original schedule.

1.3 Method of administration

Dupixent is administered by subcutaneous injection.

1.4 Pharmacological Aspects

Pharmacodynamics

Dupilumab is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. 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). IL-4 and IL-13 are the key Type 2 (including T helper type 2 [Th2]) cytokines involved in the inflammatory response in atopic

dermatitis. Thus, blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of pro-inflammatory cytokines, chemokines and IgE.

Pharmacokinetics

Absorption

Following initial subcutaneous dose of 600 mg, dupilumab reached peak mean ± SD concentrations (C_{max}) of 70.1 ± 24.1 mcg/ml by approximately 1 week post dose. Steady-state concentrations were achieved by week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly or every other week. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 73.3 ± 40.0 mcg/ml to 79.9 ± 41.4 mcg/ml for 300 mg administered every other week and from 173 ± 75.9 mcg/ml to 193 ± 77.0 mcg/ml for 300 mg administered weekly. The bioavailability of dupilumab following a subcutaneous dose is estimated to be 64%.

Distribution

The estimated total volume of distribution was approximately 4.8 ± 1.3 L.

Metabolism

The metabolic pathway of dupilumab has not been characterized.

Elimination

As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state of 300 mg every other week or 300 mg weekly dupilumab, the median times to non-detectable concentration (< 78 ng/ ml) are 10 and 13 weeks, respectively.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

Dupilumab is a fully recombinant human monoclonal antibody of the IgG4 subclass with a predicted protein molecular weight of 146,897 Da and contains a single, conserved N-glycosylation site (Asn^{302}) in the Fc region of each heavy chain subunit. Dupilumab heavy chains contain a serine to proline mutation at amino acid 233, which is located in the hinge region of the Fc domain.

Process validation activities conducted have confirmed that the dupilumab manufacturing process reproducibly produces drug substance (DS) and formulated drug substance (FDS) of consistent quality that meet predetermined specifications.

From the stability studies conducted, dupilumab DS is stable if stored at -30°C ± 10°C, protected from light for 36 months. Whereas dupilumab FDS is stable if stored at -30°C ± 10°C, protected from light for 24 months before it is shipped the drug product filling line.

2.1.2 Finished Product

Process validation conducted has shown that the manufacturing process of Dupixent is capable of consistently reproducing finished product in line with the defined specifications. The shipping validation studies have also confirmed that the product quality, asepsis, integrity and performance of the pre-filled syringes are well kept during the shipping.

The stability batches of finished product were placed on long-term stability studies (5 ± 3°C, protected from light). The stability data showed that Dupixent continued to meet the acceptance criteria for the monitored attributes after storage for 24 months. Thus, the proposed shelf-life of 24 months for this product is justified.

Dupixent is available in a 2 ml single-use pre-filled (PFS) without or with safety system (PFS-S) with a fixed 27 gauge ½ inch, thin wall stainless steel staked needle.

The product has passed the NPRA laboratory evaluation on analytical protocol and validation.

2.2 Efficacy

The proposed indication and posology for this product is supported by 11 clinical studies that have been conducted. The main pivotal studies assessed the use of Dupixent either to be used alone (SOLO 1 and SOLO 2) or to be used with topical corticosteroids (LIBERTY AD CHRONOS) in adult patients with inadequately controlled moderate-to-severe AD. The studies are summarized below:

Study Type & Design (N)	Objective of the Study	Results
SOLO 1 & SOLO 2: A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy	To demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult	**Primary efficacy results:** At week 16, significantly more patients receiving dupilumab than receiving placebo had an Investigator's Global Assessment (IGA) score of 0 (clear) or 1

Study Type & Design (N)	Objective of the Study	Results
administered to adult patients with moderate to severe atopic dermatitis (two replicate studies). *Simpson, E. L., et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375:2335-48.DOI: 10.1056/NEJMoa1610020* (N = 671 [SOLO 1]; 708 [SOLO 2])	patients with moderate-to-severe atopic dermatitis (AD).	(almost clear) and an improvement of 2 points or more on the IGA from the baseline scores. • In SOLO 1, the primary outcome occurred in 38% of patients receiving dupilumab every other week and in 37% of patients receiving weekly dupilumab, as compared with 10% of patients receiving placebo ($p < 0.001$ for both comparisons with placebo). • In SOLO 2, the primary outcome occurred in 36% of patients receiving dupilumab every other week and in 36% of patients receiving weekly dupilumab, as compared with 8% of patients receiving placebo ($p < 0.001$ for both comparisons with placebo). **Key secondary efficacy results:** In the two trials, an improvement of at least 75% on the Eczema Area and Severity Index (EASI) (EASI-75) at week 16 was reported in significantly more patients receiving each regimen of dupilumab than among those receiving placebo • SOLO 1, EASI-75 at week 16 was achieved by 51% of patients receiving dupilumab every other week, 52% of patients receiving weekly dupilumab, and 15% of patients receiving placebo ($p < 0.001$ for both comparisons with placebo). • SOLO 2, EASI-75 at week 16 was achieved by 44% of patients receiving dupilumab every other week, 48% of

Study Type & Design (N)	Objective of the Study	Results
		patients receiving weekly dupilumab, and 12% of patients receiving placebo ($p < 0.001$ for both comparisons with placebo).
LIBERTY AD CHRONOS: A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *Blauvelt, A., et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. The Lancet (2017): 389: 2287-303* (N = 740)	To assess efficacy and safety of 52 weeks of continuous treatment with two dose regimens of dupilumab (300 mg every other week or 300 mg weekly) with concomitant topical corticosteroids, with or without topical calcineurin inhibitors, in comparison to topical corticosteroids with or without topical calcineurin inhibitor, in adults with moderate-to-severe atopic dermatitis who had a previously documented inadequate response to topical medication (topical corticosteroids with or without topical calcineurin inhibitors) or systemic treatment.	**Co-primary endpoints results:** Higher proportions of patients who received dupilumab plus topical corticosteroids versus those who received placebo plus topical corticosteroids achieved both co-primary endpoints. • For one co-primary endpoint, IGA 0/1 and 2-point or higher improvement in IGA from baseline at week 16 was achieved by 39% of patients who received dupilumab weekly plus topical corticosteroids and 39% of patients who received dupilumab every other week plus topical corticosteroids versus 12% of patients who received placebo plus topical corticosteroids ($p < 0.0001$, each dose group versus placebo plus topical corticosteroids). • For the other co-primary endpoint, EASI-75 response at 16 weeks was achieved by 64% of patients who received dupilumab weekly plus topical corticosteroids and 69% of patients who received dupilumab every other week plus topical corticosteroids versus 23% of the control group ($p < 0.0001$, each dose group vs. placebo plus topical corticosteroids).

2.3 Safety

- The pooled safety analysis involving the SOLO 1, SOLO 2, and LIBERTY AD CHRONOS studies has listed adverse reactions occurred at a rate of at least 1%, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment. Those adverse reactions include injection site reaction, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. Most events were mild or moderate in intensity, transient in nature, and did not necessitate treatment discontinuation.
- No notable difference in abnormalities was observed between the placebo group and the dupilumab groups in any hematology, chemistry, urinary analysis parameters, vital signs, physical examination findings, and ECG. A decrease in LDH from above-normal mean baseline was observed in dupilumab-treated patients. However, mean values remained within the normal range over the 52 weeks.
- Overall, dupilumab was well tolerated and generally safe when used as a monotherapy or concomitantly with TCS in patients with moderate-to-severe AD. Both the 300 mg every other week and 300 mg weekly dose regimens had an acceptable safety profile, generally comparable with that of placebo.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 334th meeting on 2th May 2019 has decided to approve the registration of this product with the following indication:

Dupixent is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescriptions therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.