Cost-effectiveness of dupilumab (Dupixent®) for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy.

The NCPE has issued a recommendation regarding the cost-effectiveness of dupilumab (Dupixent®). Following assessment of the Applicant's submission, the NCPE recommends that dupilumab (Dupixent®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's Applicant's (Sanofi Ireland) economic dossier on the cost effectiveness of dupilumab (Dupixent®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **December 2019**

Summary

In March 2019, Sanofi submitted a dossier of clinical, safety and economic evidence for dupilumab (Dupixent®) for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy. Dupilumab can be used with or without topical therapies. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. IL-4 and IL-13 are critical in the initiation and maintenance of the Th2 inflammatory pathway which plays a central role in the pathophysiology of AD. Dupilumab is the first biologic drug licensed for AD. The recommended dose in adults is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given once every two weeks, administered as subcutaneous injection. Currently available systemic therapies include nonselective immunosuppressants which can be associated with severe toxicity and side effects. Patients who are refractory to other systemic treatments currently receive best supportive care (BSC) consisting of emollients, low-to-medium potency topical immunosuppressants and as-needed short-term use of rescue treatments to manage disease exacerbations.

1. Comparative effectiveness of dupilumab

Clinical effectiveness of dupilumab was examined in the LIBERTY AD clinical trial programme which included four Phase III randomised, placebo-controlled trials: SOLO 1 and SOLO 2 which were 16-week monotherapy studies; CHRONOS which was a 52-week study; and CAFÉ, a 16-week study which involved patients for whom ciclosporin had either not demonstrated adequate efficacy, had unacceptable side effects or for whom initiating ciclosporin was not medically advisable (termed “refractory” patients in the submission). Patients in the CAFÉ and CHRONOS study were treated with concomitant topical corticosteroids (TCS). The analyses of the key efficacy results of all studies show a significantly higher reduction in severity and symptoms of AD with dupilumab (with or without TCS) compared to placebo at week 16. Standard efficacy variables for AD were used to assess efficacy of dupilumab i.e. the proportion of patients with Investigator’s Global Assessment (IGA) 0 or 1 and a reduction from baseline of ≥2 points; and the proportion of patients with ≥75% improvement in the Eczema Area and Severity Index (EASI-75). Results of secondary-endpoints also indicated improvements in patient-reported symptoms, health-

related quality of life, and symptoms of anxiety and depression. Longer-term efficacy at week 52 was observed in the CHRONOS study with a significantly higher proportion of patients with EASI-75 in the dupilumab arm compared to placebo. Subgroup analyses of the SOLO and CHRONOS studies supported the efficacy demonstrated in the "refractory" population in the CAFÉ study.

The NCPE assessment focussed on the comparative efficacy of dupilumab versus BSC and versus the active comparators methotrexate and ciclosporin, the two most commonly used systemic therapies for moderate to severe AD in Ireland. Placebo data from the clinical trials were used as a proxy, however was no direct comparative efficacy data for dupilumab and active comparators. The Applicant conducted an indirect comparison of efficacy and safety of dupilumab and ciclosporin using a matching-adjusted indirect comparison (MAIC). The results of this analysis should be interpreted with caution given the paucity of data available for the comparators, the heterogeneity in methodologies between studies and the unknown level of bias which makes the results highly uncertain. There was no robust evidence on comparative efficacy of methotrexate. As a result of these limitations, in the cost-effectiveness model the Applicant assumed equivalent efficacy for active comparators to dupilumab, and assumed a more rapid discontinuation rate for comparators than for dupilumab based on literature values.

2. Safety of dupilumab

Available evidence indicates that the overall safety profile of dupilumab is mainly characterised by minor adverse reactions which were in general mild, self-limiting and manageable. The most common adverse reactions in clinical trials were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Based on the currently available data, on review of adverse events of special interest, there was no apparent increased risk of malignancy, infections, or serious cardiac, vascular, thromboembolic and ischaemic events. Long-term safety experience is limited.

3. Cost effectiveness of dupilumab

Methods

The Applicant submitted a cost-utility analysis to assess the cost-effectiveness of dupilumab compared to:

a) methotrexate or ciclosporin, in adults with moderate-to-severe AD who are candidates for systemic therapy (i.e. the full population). Included in this population is a subset of patients who had no previous experience of an immunosuppressant (i.e. immunosuppressant naïve population).
b) BSC, in adults who are not adequately controlled by topical therapies and who are contraindicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant (i.e. the "refractory" population)

The cost-effectiveness model consisted of a short-term decision-tree that reflected the initial response to treatment as shown at 16 weeks in dupilumab trials, followed by a lifetime Markov model which reflected long-term maintenance treatment of AD. A responder rule was implemented in the model to reflect the likelihood that patients who do not respond to treatment at 16 weeks, and also at 52 weeks, are likely to discontinue. Response was defined as at least a 50% reduction in the EASI score (EASI 50) from when treatment started and at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started. These data were derived from a post-hoc analysis of the dupilumab trials, according to the model population/subgroup of interest. In the full licence population, treatment response was based on the pooled SOLO 1&2, CHRONOS and CAFÉ studies. In the absence of robust evidence on the comparative efficacy of methotrexate, response was assumed equivalent to dupilumab for time-on-treatment, after which time different discontinuation rates were applied. After week 52, persistence of effect was dictated by an annual discontinuation rate. This effectively conferred much greater long-term benefit on dupilumab than methotrexate and ciclosporin, as patients were assumed to remain on dupilumab for much longer thereby retaining the benefit of treatment for longer. In the refractory population, response data was based on a pooled analysis of the CAFÉ study and a pre-specified subset of patients from the CHRONOS study which the Applicant termed "CHRONOS-CAFÉ like (CCL)". The Review Group considered that the CAFÉ trial most closely reflected real-world clinical practice given that use of TCS was not restricted in the run-in period. The NCPE Review Group identified a number of

limitations in the Applicant's approach to modelling including the use of different data sources for 52-week response in the dupilumab and BSC arms, and the use of different assumptions regarding the persistence of treatment effects in the dupilumab and BSC arms.

The primary health outcome of the model was the quality adjusted life year (QALY) as per national guidelines. Utility weights were estimated directly from the dupilumab clinical trials via a mixed-model regression whereby linear mixed models were fit to the EQ-5D-3L utility score as the response variable, controlling for age, gender and baseline EQ-5D score for each trial. A general population age adjustment to utility was applied using an additive method. A multiplicative method was considered more appropriate by the NCPE Review Group.

The model included drug acquisition costs for dupilumab and comparators, and concomitant medications (TCS and TCI). Other healthcare resources included outpatient appointments, hospitalisations, primary care visits, emergency department visits, phototherapy/psychiatry and monitoring costs.

Results

The Review Group assessment identified a number of limitations in the Applicant's base case. These limitations were addressed in the NCPE Review Group preferred base case with adjustments to the assumptions underpinning the persistence of treatment effects after 52 weeks, the source of data for treatment response and utility weightings, the age adjustment of utilities, and the discount rate. The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the NCPE's preferred base case varied depending on the population. In the full population, plausible ICERs ranged from €103,175-€136,062 per QALY. In the "refractory" population, plausible ICERs ranged from €74,401-€83,424 per QALY. Analysis of the outcomes for the various populations in the economic model demonstrated that 94%-100% of the QALYs gained with dupilumab versus comparators occurred after the period for which data was observed in clinical trials (i.e. after 52 weeks). It should be noted that beyond 52 weeks, there is no robust clinical evidence on the comparative efficacy of dupilumab, and all efficacy outcomes are based on extrapolations and assumptions. Using the NCPE preferred base case, at a cost-effectiveness threshold of €20,000 and €45,000 per QALY the probability of cost-effectiveness is 0%. In the Applicant

base case, the ICERs were €93,692 per QALY and €66,039 per QALY in the full population and the "refractory" population respectively with probabilities of cost-effectiveness of 0%-0.1% at cost-effectiveness thresholds of €20,000 and €45,000 per QALY.

4. Budget impact of dupilumab

Dupilumab is submitted for reimbursement under the High Tech Drug Arrangement. The price to wholesaler of two dupilumab 300mg prefilled syringes is €1,153.85. The total annual cost to the HSE including wholesale mark-up, rebates and fees is €19,911 per patient including VAT. Based on the Applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €51.9 million in the full population and €38.3 million in the "refractory" population. The Applicant's budget impact analysis relates only to adults with AD, the population in which dupilumab was first licensed. Subsequent license extensions include adolescents with AD, adults and adolescents with severe asthma and adults with severe chronic rhinosinusitis with nasal polyposis. These additional indications are expected to increase the budget impact significantly.

5. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that dupilumab be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.