Cost-effectiveness of secukinumab (Cosentyx®) for the treatment of moderate to severe plaque psoriasis

The NCPE has issued a recommendation regarding the cost-effectiveness of secukinumab (Cosentyx®). Following NCPE assessment of the applicant's submission, secukinumab (Cosentyx®) is not considered cost-effective for the treatment of moderate to severe plaque psoriasis and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Novartis Ireland Ltd) economic dossier on the cost effectiveness of secukinumab (Cosentyx®). 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.

National Centre for Pharmacoeconomics **September 2015**

In April 2015, Novartis Ireland Ltd submitted a dossier of clinical, safety and economic evidence in support of secukinumab for the treatment of moderate to severe plaque psoriasis. Secukinumab is a first in class, fully human monoclonal antibody that selectively targets the pro-inflammatory cytokine interleukin-17a. Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Secukinumab can therefore be used first, second or third line as an alternative to traditional systemic therapies, as an alternative to currently available biologics following failure of traditional systemic therapy, or as an additional option following failure of a biologic therapy. The recommended dose of secukinumab is 300 mg by subcutaneous injection at Weeks 0, 1, 2 and 3, followed by monthly dosing starting at Week 4.

1. **Comparative effectiveness of secukinumab**

- The relevant comparator for the pharmacoeconomic evaluation of secukinumab depends on the stage of the treatment pathway. Current standard of care for first line treatment among patients with moderate to severe psoriasis consists of traditional systemic therapies (methotrexate, fumaric acid esters, acitretin, ciclosporin, phototherapy alone or in combination). Biologic therapies are used in the second line setting, following failure of traditional non-biologic systemic therapies. In Ireland, the biologic therapies etanercept, adalimumab and ustekinumab are used more commonly than infliximab. In the third line setting (i.e. failure to respond to a biologic), a second biologic may be considered.
- In an analysis of pooled randomised controlled trials, secukinumab was superior to placebo and etanercept at Week 12 with respect to the co-primary clinical endpoints, PASI 75 response (79.4% vs. 44.0% etanercept, 4.2% placebo) and IGA 0/1 response (65.0% vs. 27.2% etanercept, 2.2% placebo). This response was sustained up to Week 52 in 78%-81% of patients treated with secukinumab in clinical trials, and in 78% of patients treated with etanercept. In the CLEAR study, PASI 90 response for secukinumab was superior to ustekinumab at week 16 (57.6% vs 57.6%).
- A network meta-analysis was conducted by the applicant to estimate comparative efficacy of secukinumab and biologic comparators. PASI outcomes at week-12 for secukinumab/ustekinumab/etanercept, week-10 for infliximab and week 16 for adalimumab, were combined from 26 placebo-controlled and direct-comparative

studies The results of the network meta-analysis showed that all treatments had significantly better PASI 50, 75 and 90 responses than placebo, and that secukinumab had higher probabilities of PASI response compared with etanercept 25mg, adalimumab and ustekinumab 45mg, and equivalent efficacy compared with ustekinumab 90mg and infliximab.

2. Safety of secukinumab

- The most frequently reported adverse drug reactions with secukinumab in placebo-controlled phase III studies were upper respiratory tract infections, most frequently nasopharyngitis rhinitis, and these were mostly mild or moderate.
- Non-serious mucocutaneous candida infections, mild ear canal and Herpes simplex infections, conjunctivitis and gastrointestinal symptoms, mainly diarrhoea, and neutropenia were reported more frequently with secukinumab than placebo in the psoriasis clinical studies.
- Discontinuation due to adverse events was 3.26%, 3.7% and 1.4% for secukinumab, etanercept and placebo respectively across studies.
- No particular safety concerns have been raised compared to other systemic treatments available for the treatment of psoriasis. The long-term safety of secukinumab in unknown.

3. Cost effectiveness of secukinumab

Methods

- A cost-utility analysis, comparing secukinumab with etanercept, adalimumab and ustekinumab from the perspective of the Irish Health Services Executive, was submitted by the applicant. The population was restricted to patients with moderate to severe psoriasis who have failed traditional systemic therapy and are eligible for treatment with a biologic therapy. This approach essentially restricted use of secukinumab to the second and third line setting, ignoring its role as a first line therapy. Infliximab was also omitted among comparators due to the current infrequent use of this therapy for psoriasis in Ireland. The applicant was requested to include conventional therapy as a comparator in the model but this was not done.

- The economic model combined a decision tree for the first year, and a Markov state-transition model for subsequent years. All patients received treatment for the induction period (12 weeks for secukinumab, etanercept, and ustekinumab, and 16 weeks for adalimumab), at which point the response to treatment was assessed and only treatment responders (defined as achieving a PASI 75 or higher response) remained on treatment. The NCPE had concerns regarding the automatic stopping-rule for non-responders, including those who experienced a "partial" response. The product license states that consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment, but adds that some patients with initially partial response may subsequently improve with continued treatment beyond 16 weeks. The benefits and costs of continuing treatment in partial responders was not captured in the applicant's mdel. PASI response achieved during the 12-week induction phase was assumed to be maintained for the duration of the model time horizon (i.e. up to ten years). Non-responders to induction therapy and patients who discontinued treatment at any stage (11.7% in year 1, 20% in subsequent years) were assumed to transition to the PASI<50 health state and receive best supportive care comprising either methotrexate, ciclosporin or no drug treatment. The model structure did not facilitate second and subsequent-line biologic therapies. Comparative efficacy data were derived from the network meta-analysis for the comparison with adalimumab and ustekinumab, and directly from the FIXTURE trial for etanercept. The NCPE had concerns regarding the exclusion of additional evidence for etanercept, and the exclusion of the lower induction dose of 25mg twice weekly. Following a request from the NCPE review team the applicant submitted a comparison between secukinumab and etanercept 25mg based on the results of the network meta-analysis.
- Health benefits were measured in quality-adjusted life years (QALYs) and captured utilities associated with PASI health states. No utility adjustments were made for adverse events. Health state increments for use in the model were based on a regression model of change in EQ-5D from baseline in secukinumab clinical trials, using PASI response and baseline DLQI as covariates. The NCPE had concerns regarding the omission of adverse events in the model, however most adverse

events in secukinumab clinical trials were infrequent and mild or moderate in severity and probably unlikely to have a major impact on cost-effectiveness.

- The model applied treatment-specific drug-acquisition, monitoring, adverse-event costs, physician visit, hospitalisation and phototherapy costs. The costs of serious adverse events were omitted during the first year of biologic treatment in the applicant's model. High-tech patient care fee costs were also omitted from the model. The number of administrations of ustekinumab was based on calendar years rather than annual cycles. NCPE analysis updated the model costs to include high-tech costs, ustekinumab costs based on annual cycles and the cost of serious adverse events. The annual cost of secukinumab depends on the frequency of administration, as the licensed posology of "monthly maintenance" could be interpreted as every four weeks (the dosing schedule used in the secukinumab clinical trials) or once every calendar month, i.e. 13 versus 12 annual administrations. Both dosing scenarios are considered in the cost-effectiveness analysis.

Results

- The probabilistic incremental cost-effectiveness ratios (ICERs) for secukinumab compared with comparators were €68,423/QALY (ustekinumab 45 mg), €81,748/QALY (ustekinumab 90 mg), €72,575/QALY (adalimumab 40 mg), €80,147/QALY (etanercept 25mg using data from the network meta-analysis) and €73,889/QALY (etanercept 50mg using data from FIXTURE and deterministic analysis –probabilistic analysis was not possible due to missing data). The probability of cost effectiveness at a willingness to pay threshold of €45,000/QALY was 7% compared with ustekinumab 90mg and 0% compared with all other comparators.

Sensitivity analysis

- The uncertainty associated with the ICERs was explored using one-way sensitivity analyses and additional scenario analyses in which an alternative source of utility values, alternative induction durations for secukinumab and a longer time horizon were applied. The cost of biologic therapy and the number of annual secukinumab administrations were the main drivers of cost-effectiveness. Assuming 13 doses of secukinumab annually rather than 12, increased the ICER in all cases, ranging from €87,358/QALY compared with etanercept 50mg to €168,801/QALY compared with

ustekinumab 90mg.

4. Budget impact of secukinumab

Secukinumab is submitted for reimbursement under the High-tech drug scheme. The proposed ex-manufacturer price of secukinumab 300mg is €1,118 per unit. The annual cost per patient ranges from €18,030 to €19,470 depending on the frequency of administration. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €30 million (€1.8 million in year 1 rising to ~€11.5 million in year 5). The applicant highlighted the potential for drug cost-offsets from the displacement of other biologic therapies which would otherwise have been prescribed, leading to a net budget-impact of €45,702 in year 1, rising to €237,378 in year 5. This analysis ignored the potential for secukinumab to be used in the first-line setting prior to alternative biologic therapy, and in sequence with other therapies, instead of displacing them. In these scenarios the net budget impact would be much greater.

5. Conclusion

Secukinumab is an additional therapeutic option across the treatment pathway of moderate to severe psoriasis. The applicant restricted the cost-effectiveness analysis to the second and third line setting, following failure of traditional systemic therapy. As a result, a recommendation on the cost-effectiveness of secukinumab in the complete licensed population cannot be made on the basis of this submission. ICERs versus all comparators were higher than the willingness to pay threshold of €45,000/QALY and heavily dependent on the frequency of secukinumab administration. Following NCPE assessment of the company submission, reimbursement of secukinumab (Cosentyx®) is not recommended for the treatment of adult patients with moderate to severe psoriasis at the submitted price.