Cost-effectiveness of apremilast (Otezla®) alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs) for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy

The NCPE has issued a recommendation regarding the cost-effectiveness of apremilast (Otezla®). Following NCPE assessment of the applicant's submission, apremilast (Otezla®) is not considered cost-effective for the treatment of active psoriatic arthritis 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 (Celgene Ltd) economic dossier on the cost effectiveness of apremilast (Otezla®). 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   **April 2016**

In September 2015, Celgene Ltd submitted a dossier of clinical, safety and economic evidence in support of apremilast, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 that works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators implicated in PsA. The recommended dose of apremilast is 30 mg twice daily taken orally.

1. **Comparative effectiveness of apremilast**

- The comparator for apremilast is current standard of care which includes the systemic biologic therapies etanercept, adalimumab, infliximab, golimumab, certolizumab (TNF-α antagonists) and ustekinumab (IL 12/23 antagonist). Non-biologic conventional DMARD therapy (e.g. methotrexate, leflunomide) may also be a comparator of interest, to reflect the potential for patients to switch between conventional DMARDs following failure of initial therapy.

- In a pooled analysis of three placebo-controlled, randomised trials (PALACE 1, 2 and 3), a significantly greater proportion of patients receiving apremilast achieved the primary outcome (modified ACR20 (mACR)) at Week 16 compared with placebo (37% vs 19%, $p \leq 0.0001$). Apremilast was associated with statistically significant improvements in the proportion of patients achieving a PsARC response (49% vs 30%, $p \leq 0.0001$). A minimal clinically important difference of equal to or greater than 0.30 in the HAQ-DI score was achieved in 36.4% patients in the active arm compared to 26% in the placebo arm ($p \leq 0.001$). Approximately 65% of patients were treated with concomitant DMARDs. The studies did not include endpoints to show the impact of apremilast on progression of structural changes.

- A network meta-analysis was conducted by the applicant to estimate comparative efficacy of apremilast and biologic comparators. The results showed that apremilast demonstrated the lowest absolute response for all outcomes (PsARC, ACR, PASI and HAQ-DI) compared with all other active treatments. The clinical trials or network meta-analysis did not compare apremilast with conventional systemic non-biologic DMARD therapies.

2. Safety of apremilast

- The most commonly reported adverse reactions in Phase 3 clinical studies were gastrointestinal disorders including diarrhoea (15.7%) and nausea (13.9%). These were mostly mild to moderate in severity, occurred within the first 2 weeks of treatment and usually resolved within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%). A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. Patients who are underweight at the start of treatment should have their body weight monitored regularly.

3. Cost effectiveness of apremilast

Methods

- A cost-utility analysis, comparing treatment sequences with and without apremilast from the perspective of the Irish Health Services Executive, was submitted by the applicant. The apremilast sequence included apremilast as a pre-biologic therapy followed by a sequence of two biologics (adalimumab and etanercept) and best supportive care (BSC). Golimumab and ustekinumab were also included in scenario analysis. The analysis utilised a Markov state-transition cohort model with a 40-year time horizon. All patients received treatment for the trial period (16 weeks for apremilast, 12 weeks for all other biologic comparators), at which point the response to treatment was assessed and only treatment responders (defined as achieving a PsARC response) remained on treatment, while non-responders discontinued initial therapy and initiated a trial period of the next treatment in the sequence. Patient failing to achieve a response to trials of the defined biologic therapies in the sequence proceeded to BSC. With this approach, the additional benefits and costs of one extra active therapy were accrued in the apremilast arm, delaying the costs and benefits of biologic therapies and BSC. It is anticipated that apremilast will primarily be used as a pre-biologic therapy, however there is considerable uncertainty associated with the number and constituents of the subsequent sequence of biologic therapies following failure of apremilast. Separate scenarios were conducted in which apremilast replaced the first biologic in the treatment sequence allowing sequences of equal length to be compared.

- The NCPE review team had a number of concerns regarding the model submitted by the applicant. Evidence of efficacy is limited to short-term outcomes (up to 16 weeks) while the model assumes that efficacy in PsARC response, PASI scores and HAQ-DI scores continues indefinitely while patients remain on therapy. The biologic therapies have been shown to reduce the rate of progression of peripheral joint damage, but there is no radiographic evidence of a similar disease modifying effect with apremilast. Reduced efficacy of the second treatment in the comparator sequence (by a factor of 2.7) was assumed following primary non-response to the first treatment in the comparator sequence, to reflect a decline in response to TNF-α antagonists with sequential use. This assumption was not applied in the apremilast sequence, conferring a significant advantage on apremilast.

- Health benefits were measured in quality-adjusted life years (QALYs) and captured utilities associated with PsARC, PASI response and HAQ-DI scores. No utility adjustments were made for adverse events. EQ-5D utilities were based on a multivariate linear regression model estimated using the pooled apremilast data and responses obtained from the applicant's network meta-analysis. The NCPE had concerns regarding the omission of adverse events in the model, given the prevalence of adverse events with apremilast, particularly gastrointestinal disorders, during the initial treatment period.

- The model applied treatment-specific drug acquisition, administration and monitoring costs, and healthcare costs associated with PsA, psoriasis and BSC. Healthcare costs were assumed to increase with the severity of the disease, as a function on the HAQ-DI score.

Results

- The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case apremilast sequence (apremilast>adalimumab>etanercept>best supportive care) compared with the base case comparator sequence (adalimumab>etanercept>best supportive care) was €33,476/QALY. A detailed analysis of the cumulative QALYs over time revealed that the QALY gain in the apremilast arm is entirely due to the presence of one additional active therapy. The probability of PsARC and PASI responses with apremilast (already much lower than the biologic therapies) could be reduced to 0% and the economic model would still

calculate more QALYs with the apremilast sequence than the shorter comparator sequence. The face validity of this approach is therefore questionable.

- In the scenario where apremilast is a replacement for the first treatment in the sequence, the apremilast sequence may be less costly and less effective (replacing etanercept at its originator price), more costly and less effective (assuming a reduced price for etanercept consistent with biosimilar pricing) or less costly and more effective (replacing adalimumab). In these three comparisons, apremilast becomes less costly and less effective when the assumption of reduced efficacy of a second biologic therapy is removed.

- A scenario in which apremilast was compared with non-biologic conventional therapy was explored by the NCPE review team, assuming the costs of methotrexate and leflunomide and (conservatively) the efficacy of placebo. In this scenario the ICERs ranged up to €70,779/QALY, however the robustness of this analysis was limited due to lack of data and reliance on assumptions for both cost and efficacy.

Sensitivity analysis

- The uncertainty associated with the ICERs was explored using one-way sensitivity analyses and additional scenario analyses. The HAQ-DI increase per cycle in patients receiving BSC was the main driver of cost-effectiveness. The HAQ-DI coefficients for the cost and HRQoL regression models and discount rates were the next most influential parameters. The findings of the deterministic sensitivity analysis illustrate the importance of the assumptions regarding HAQ-DI progression in the model.

- The assumption that apremilast halts underlying HAQ-DI progression is not supported by evidence from apremilast clinical trials. This assumption could not be changed directly due to the structure of the applicant's model, but it is clear that the cost effectiveness of apremilast would be significantly less favourable if this assumption was removed.

4. Budget impact of apremilast

- Apremilast is submitted for reimbursement under the High-tech drug scheme. The price of apremilast is lower than the biologic comparators and substantially higher than conventional non-biologic systemic therapies. The proposed ex-manufacturer price of apremilast is €759 per 28-day pack (56x30mg tablets). The annual

reimbursement cost is €11,041. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €3.6 million (€34,364 in year 1 rising to €1.4 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 net savings. The magnitude of the applicant's predicted savings is inconsistent with the positioning of apremilast as an additional line of therapy rather than as a displacement therapy.

5. Conclusion

- The cost-effectiveness of apremilast is dependent on the sequence and efficacy of subsequent biologic therapies used after treatment failure. There is considerable uncertainty associated with this sequence and apremilast is not cost-effective in all circumstances. The cost effectiveness of apremilast is also dependent on the assumption that it halts radiographic disease progression, which has not been demonstrated in clinical trials. Following NCPE assessment of the company submission, reimbursement of apremilast (Otezla®) is not recommended for the treatment of adult patients with active PsA at the submitted price.