**Cost-effectiveness of apremilast (Otezla®) for the treatment of moderate to severe chronic plaque psoriasis in adult patients who have failed to respond to, or who have a contraindication to or are intolerant to other systemic therapies including cyclosporine, methotrexate or psoralen and ultraviolet A light (PUVA)**

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 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 (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** **January 2016**

In July 2015, Celgene Ltd submitted a dossier of clinical, safety and economic evidence in support of apremilast for the treatment of moderate to severe chronic plaque psoriasis in adult patients who have failed to respond to, or who have a contraindication to or are intolerant to other systemic therapies including cyclosporine, methotrexate or psoralen and ultraviolet A light. 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 psoriasis. 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 systemic biologic therapies etanercept, adalimumab, infliximab (TNF-α antagonists) and ustekinumab (IL 12/23 antagonist). Non-biologic conventional therapy may also be a comparator of interest, to reflect the potential for patients to switch between conventional therapies following failure of initial therapy.
- In two placebo-controlled, randomised trials (ESTEEM 1 and 2), a significantly greater proportion of patients receiving apremilast achieved a 75% reduction in PASI score (PASI-75) at Week 16 compared with placebo (23.0%-27.8% difference in proportions $p<0.001$). Response rates for patients originally randomised to apremilast peaked around Week 16 and were generally maintained through Week 32. A considerable number of patients lost PASI-75 response with continued treatment up to 52 weeks (51.9% in ESTEEM 1) although the patient numbers were low and the majority maintained PASI response levels of 70-74. A network meta-analysis was conducted by the applicant to estimate comparative efficacy of apremilast and biologic comparators. The results showed that all biologic treatments had significantly better PASI-50, -75 and -90 responses than apremilast. The clinical trials or network meta-analysis did not compare apremilast with conventional systemic non-biologic 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 (etanercept and adalimumab) and best supportive care (BSC). Infliximab and ustekinumab were also included in scenario analysis. The analysis utilised a Markov state-transition cohort model with a ten-year time horizon. All patients received treatment for the induction period (16 weeks for apremilast, adalimumab and ustekinumab, 12 weeks for etanercept and 10 weeks for infliximab), 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, 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 crucially delaying the costs of 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. Non-biologic conventional therapy was not included as a comparator.
- The NCPE review team had a number of concerns regarding the comparative efficacy data included in the applicant's economic analysis. A placebo response was assumed in patients receiving BSC based on rates presented by the national clinical guideline

centre in the UK. This was considered by the NCPE review team to be a conservative assumption which may underestimate the efficacy of BSC. The efficacy of the biologic therapies in the second, third, fourth etc. positions of the treatment sequences was assumed to be equivalent to the efficacy at the first position of the sequence. There is little evidence to support this assumption, and limited evidence to suggest reduced efficacy of second-line biologic therapies in psoriasis. PASI response achieved during the trial period was assumed to be maintained for the duration of the model time horizon, despite evidence of loss of response from the clinical trials. This was accounted for by a long-term annual withdrawal rate of 20% for apremilast and biologic therapies.

- 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 week 16 EQ-5D data collected in patients receiving apremilast in the ESTEEM 1 and 2 trials. 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, monitoring, and healthcare costs associated with outpatient physician visits and hospitalisation costs. The costs of BSC were based on a "high-need", highly resource-intensive population in the UK which may not be representative of the Irish population and which was considered by the NCPE review team to overestimate costs.
- Included in the NCPE review team's preferred set of assumptions (applied in the results presented below) were: placebo response from the applicant's network meta-analysis in patients receiving BSC; withdrawal rate of 23.8% to more closely reflect the apremilast clinical trials; and use of Irish sources for hospitalisation costs.

*Results*

- The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case apremilast sequence (apremilast>etanercept>adalimumab>best supportive care) compared with the base case comparator sequence (etanercept>adalimumab>best supportive care) was €26,697 increasing to €33,649 assuming a reduced price for etanercept consistent with biosimilar pricing. As a

replacement therapy, where apremilast replaces etanercept in a sequence followed by adalimumab>ustekinumab>BSC, apremilast is less costly and less effective assuming the originator price for etanercept, but becomes dominated i.e. more costly and less effective, when the reduced price for etanercept is assumed. In other sequences which don't include etanercept, as a replacement therapy apremilast remains less costly and less effective with ICERs ~€70,000 per QALY lost. 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 ciclosporin and (conservatively) the efficacy of placebo. In this scenario the ICERs ranged up to €59,283/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 cost of BSC and the baseline utility score were the main drivers of cost-effectiveness in one-way sensitivity analysis. Alternative sources of BSC efficacy and cost, etanercept pricing, and discontinuation rates had the greatest impact on the ICERs in scenario analyses.

**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 €6.1 million (€107,000 in year 1 rising to 2.25 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 in the applicant's submission is dependent on the sequence of biologic therapies used after treatment failure and assumptions associated with the efficacy and cost of this sequence. There is considerable uncertainty associated with this sequence and apremilast is not cost-effective in all circumstances. Following NCPE assessment of the company submission, reimbursement of apremilast (Otezla®) is not recommended for the treatment of adult patients with moderate to severe psoriasis at the submitted price.