Cost Effectiveness of Pomalidomide *(*Imnovid®*)* for the Treatment of Refractory or Relapsed and Refractory Multiple Myeloma

The NCPE has issued a recommendation regarding the use of pomalidomide for this indication. The NCPE does not recommend reimbursement of pomalidomide.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (Celgene) economic dossier on the cost effectiveness of pomalidomide. 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 that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that 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 **March 2015**

Summary

Celgene submitted a dossier for pomalidomide (Imnovid®) on 19 March 2014. Final changes were received from Celgene in December 2014. Pomalidomide in combination with dexamethasone is indicated for the treatment of adult patients with refractory or relapsed and refractory multiple myeloma who have received at least two previous treatment regimens, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy (i.e. for third line treatment). Pomalidomide (POM) belongs to the same class of immunomodulatory drugs as lenalidomide and is a structural derivative of thalidomide (THAL).

The recommended starting dose is 4mg to be taken orally once daily on days 1 to 21 of repeated 28-day cycles. Dose interruptions and reductions for POM are required if neutropenia or thrombocytopenia occur.

1. Comparative Effectiveness

- At present, no comparator drugs or drug combinations are specifically licensed in Ireland for third line treatment of patients with multiple myeloma. In addition, there is no clear standard of care in this setting. The comparators included in the pharmacoeconomic evaluation included high dose dexamethasone (HiDEX), which is the only treatment for which direct comparative evidence compared to POM+LoDEX (low dose dexamethasone) is available. However, HiDEX is generally given in Ireland as palliative care following the failure of other active treatment options. Other comparators used in the evaluation included bortezomib + lenalidomide + dexamethasone (BOR+LEN+DEX), bortezomib + dexamethasone (BOR+DEX) and lenalidomide + dexamethasone (LEN+DEX).
- The evidence submitted to support efficacy was a phase 3, multicentre, open-label, randomised controlled trial (MM-003) (N=455) comparing the efficacy and safety of POM+LoDEX (n=302) with HiDEX (n=153) in patients with refractory or relapsed and refractory multiple myeloma. The primary outcome was progression-free survival (Independently assessed) with a secondary analysis performed for overall survival, time to progression and time to treatment failure. Following the pre-planned cut-off date (Sept 2012) for progression-free survival, patients in the HiDEX arm could switch to the

pomalidomide arm. This resulted in approximately 50% of patients switching treatments. The cut-off date for estimation of overall survival was March 2013.

- The unadjusted median overall survival was 54 weeks (95% CI 45.3, 66.4) for POM+LoDEX versus 35 weeks (95% CI 29.9, 39.1) for HiDEX, HR 0.70 (95% CI 0.54, 0.92). The median overall survival for HiDEX was 25 weeks once adjusted for crossover (95% CI; 18.3, 32.6), HR 0.52 (95% CI 0.39, 0.68). The median progression-free survival was 16 weeks (95% CI 13.0, 19.6) for POM+LoDEX versus 8.1 weeks (95% CI 7.1, 9.4) for HiDEX, HR 0.49 (95% CI 0.39, 0.61) (March 2013). The Review Group noted that crossover was not adjusted for this outcome; however the pre-crossover data was broadly in line with the post-crossover data. The median time to treatment failure in the POM+LoDEX arm was 12.4 weeks (95% CI: 11.9, 16.1) and 8.0 weeks (95% CI: 4.9, 8.3) in the HiDEX arm, HR 0.48 (95% CI: 0.39, 0.60).
- The comparative efficacy data was derived from an indirect treatment comparison for the BOR+LEN+DEX, BOR+DEX and LEN+DEX comparators. The NCPE review team however is concerned that potentially relevant studies may have been omitted. Furthermore, the studies that were included were of a lesser quality of evidence (retrospective, chart review) and contained small patient numbers. In addition, the patient populations were not directly comparable to the MM-003 population..

2. Safety

- The most frequently reported treatment emergent adverse events, associated with POM, in the clinical trial (MM-003) were: neutropenia, anaemia, thrombocytopenia and fatigue. The most frequently occurring serious adverse events in both treatment arms (POM+LoDEX and HiDEX) were pneumonia and general physical health deterioration.
- Multiple myeloma was the most common cause of death in both arms. A total of 146/300 (48.7%) of patients died in the POM arm, 100/300 (33.3%) from multiple myeloma. A total of 84/150 (56%) of patients died in the HiDEX arm, 52/150 (34.7%) from mutliple myeloma. There were 11 treatment-related deaths in the POM+LoDEX arm: eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one nervous system disorder. There were seven treatment related deaths in the HiDEX arm: all infections and infestations.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing POM+LoDEX with each of the four comparators was submitted by the applicant. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility Markov model, incorporating three health states: pre-progression/stable disease, post-progression/progressive disease and death.
- The time horizon of the model was 25 years. The NCPE Review Group believe that this is too long given the late stage of multiple myeloma represented by third line therapy.
- Health benefit was measured in quality adjusted life years (QALYs). Utility values were derived from health related quality of life data collected in the MM-003 trial and included health state utilities and utility decrements for adverse events. Costs included drug acquisition, administration, health state costs and costs associated with adverse events and end of life care (the cost of which was considered to be low by the Review Group). Other costs such as cost of renal failure were not included.
- The main efficacy outcomes used in the model were overall survival, progression free survival and time to treatment failure.

Results

- The ICER for POM+LoDEX is €102,485/QALY (incremental cost and QALYs €59,527; 0.58 respectivelycompared with HiDEX,
- The ICER for POM+LoDEX compared to BOR+LEN+DEX is €50,657/QALY (incremental cost and QALYs €40,697 and 0.80 respectively).
- The ICER for POM+LoDEX compared to BOR+DEX is €43,525/QALY (incremental cost and QALYs €36,320 0.83 respectively).
- The ICER for POM+LoDEX compared to LEN+DEX is €51,886/QALY (incremental cost and QALYs €43,068 and 0.83 respectively)

Sensitivity analysis

- One way sensitivity analyses were performed. The model was most sensitive to the choice of parametric survival curves and the utility values used.
- Applying treatment discontinuation based upon the progression-free survival curve rather than time to treatment failure increased the ICERs for

all comparators.

- The probability of cost effectiveness at a threshold of €45,000/QALY was estimated as 0% for the HiDEX comparison, 64% compared to BOR+LEN+DEX, 36% compared to BOR+DEX and 13% compared to LEN+DEX.

4. Budget Impact Analysis

At the requested ex-factory price of €9,605.58 per 28-day pack (21 4mg capsules), the projected gross budget impact, based on company estimates of market share, is €15.2 million over the first 5 years; €6,59 million (year 1), €2,427,991 (year 2), €2,079,165 (year 3), €2,021,541 (year 4) and €2,108,570 (year 5). If alternative dosage assumptions for POM are assumed the cumulative gross budget impact could increase to €22.5 million.

The cumulative net-budget impact over 5 years (including drug cost offsets from the weighted average displacement of other drugs (BOR+LEN+DEX 65%, BOR+DEX 18% and LEN + DEX 17%) was estimated as €5.6 million. There is minimal cost offset for dexamethasone.

5. Conclusion

POM+LoDEX is indicated for the treatment of adult patients with refractory or relapsed and refractory multiple myeloma who have received at least two previous treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. At present, no comparator drugs or drug combinations are specifically licensed in Ireland for third line treatment of patients with multiple myeloma. The only direct evidence available is for POM+LoDEX versus HiDEX, and POM was not shown to be cost effective in this comparison.

The estimated efficacy versus other commonly used treatments (BOR+LEN+DEX, BOR+DEX and LEN+DEX) was derived from an indirect comparison. The efficacy outputs from this indirect treatment comparison are subject to a great deal of uncertainty.

Following NCPE assessment of the company submission, reimbursement of pomalidomide (Imnovid®) is not recommended at the current price for the treatment of adult patients with refractory or relapsed and refractory multiple myeloma that have received at least two previous treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.