Cost-effectiveness of Daratumumab (Darzalex®) for the Treatment of Adult Patients with Relapsed and Refractory Multiple Myeloma.

The NCPE has issued a recommendation regarding the cost-effectiveness of daratumumab (Darzalex®). Following NCPE assessment of the applicant's submission, daratumumab (Darzalex®) is not considered cost-effective for the treatment of adult patients with relapsed and refractory multiple myeloma and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Janssen-Cilag) economic dossier on the cost effectiveness of daratumumab (Darzalex®). 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 **March 2017**

Summary

In October 2016, Janssen-Cilag submitted a dossier for daratumumab (Darzalex®). Daratumumab as monotherapy is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (R/RMM), whose prior therapy included a protease inhibitor (PI) and an immunomodulatory agent (IMiD) and who have demonstrated disease progression on the last therapy. Daratumumab is a human monoclonal antibody that targets CD38.

1. **Comparative effectiveness of Daratumumab (Darzalex®)**

- The comparator included in the pharmacoeconomic evaluation is pomalidomide plus dexamethasone which is the only treatment licensed and reimbursed in Ireland as third line therapy for multiple myeloma (MM). The NCPE review team has concerns that bortezomib plus lenalidomide plus dexamethasone should also have been included as this is the most widely used third line treatment option in clinical practice in Ireland.
- Currently there are no comparative clinical trials of daratumumab monotherapy in patients with R/RMM. The evidence to support efficacy was based on the patient cohorts receiving daratumumab 16mg/kg from two phase II, open label studies of daratumumab monotherapy (MMY2002 and GEN501). MMY2002 evaluated daratumumab in R/RMM patients previously treated with at least three lines of therapy (including a PI and an IMiD) or who were refractory to both a PI and an IMiD. GEN501 enrolled patients with relapsed MM or relapsed MM that was refractory to two or more lines of prior therapy. The trials were considered sufficiently similar to directly pool the data. The primary efficacy endpoint in MMY2002 was the overall response rate (ORR). Secondary endpoints included; duration of response (DoR), time to response (TTR), progression-free survival (PFS), time to disease progression (TTP), overall survival (OS) and clinical benefit rate. The primary endpoint in the GEN501 study was safety; the primary efficacy endpoint was ORR. Secondary endpoints included objective response, TTP, DoR, PFS and OS. The NCPE review team has concerns that the lack of comparative data means that it is not possible to assess the magnitude of effect of daratumumab compared with other available therapies.

In addition, HRQoL data was not collected which is essential to understand the patient experience with daratumumab.

- Pooled analysis of the MMY2002 and GEN501 studies showed a median PFS of 4.0 months (95% CI 2.8, 5.6) and a median OS of 20.1 months (95% CI 16.6, not evaluable) for daratumumab 16mg/kg patients. With an ORR of 31.1% (95% CI 23.7, 39.2) and a median time to response of 0.95 months (0.5 – 5.6 months). The NCPE review team has concerns regarding the immaturity of the results.
- The comparative efficacy data underpinning the company's economic model was derived by fitting parametric curves to survival data from an indirect treatment comparison of daratumumab monotherapy versus pomalidomide plus dexamethasone, as direct comparative evidence was unavailable for these treatment regimens. The NCPE review team however has some concerns regarding the level of uncertainty introduced by the indirect treatment comparison, especially in relation to the use of real world patient data for the pomalidomide cohort in preference to available clinical trial data.

2. Safety of daratumumab (Darzalex®)

- Infusion related reactions were the most frequently observed treatment emergent adverse events with daratumumab. Other common treatment emergent adverse events included fatigue, nausea, anaemia, back pain, cough, thrombocytopenia, upper respiratory tract infection and neutropenia.
- The most common cause of death was progressive disease.

3. Cost effectiveness of daratumumab (Darzalex®)

Methods

- A cost-utility analysis comparing daratumumab monotherapy with pomalidomide plus dexamethasone was submitted by the company. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility Markov model, incorporating three health states: pre-progression, post-progression and death.
- The time horizon was 15 years (reflecting a life-time horizon), with cycle lengths of 1 week.

- Health benefit was measured in quality adjusted life years (QALYs). Utility values for the pre-progression and post-progression health states were identified from a review of the literature. Utility decrements for adverse events were also included in the model.
- Costs included drug costs, drug administration, concurrent medication costs, as well as monitoring costs, costs of treating adverse events and end-of-life costs.
- Treatment specific survival curves modelling PFS and OS were used to inform treatment effectiveness in the model. Parametric curves were fitted to the survival data from the pooled MY2002 and GEN501 data for daratumumab monotherapy. Hazard ratios were applied to the daratumumab curves to obtain PFS and OS curves for the pomalidomide plus dexamethasone comparison. These hazard ratios were derived based on a matching analysis using a real world cohort. The NCPE review team has some concerns regarding the use of the real world data in preference to available clinical trial data for the comparator. Furthermore, there are concerns regarding the uncertainty in the appropriate choice of OS curve.

Results

- The original base case presented by the company estimates an incremental cost of €34,352 for the gain of 0.68 QALYs. This results in an ICER of €50,201 per QALY. A revised base case supplied by the company containing several modifications requested by the NCPE, resulted in an ICER of €49,886 per QALY.

Sensitivity analysis

- One way sensitivity analyses were performed with model input parameters varied across their plausible ranges. The results were most sensitive to PFS and OS hazard ratios for daratumumab versus pomalidomide plus dexamethasone, drug acquisition costs and utility weights associated with time spent pre- and post-progression.
- A number of alternative scenarios were considered. The NCPE review team has particular concerns regarding the appropriate choice of survival curve used to assess OS. Scenario analyses show that the use of differing curves results in ICERs between €34,022 and €57,641 per QALY. The cost utility results were also sensitive to

scenarios assuming mortality hazards equal for both treatments after follow-up and the price of pomalidomide.

- An analysis based on the NCPE preferred set of assumptions, which included relative effectiveness based on clinical trial results in preference to real world data and an equal hazard ratio applied to both treatments following the end of follow up, resulted in an incremental cost of €39,334 for the gain of 0.31 QALYs, yielding an ICER of €127,785 per QALY.
- The probabilistic ICER did not differ greatly from the deterministic ICER. The probability of cost-effectiveness at a threshold of €45,000 per QALY was estimated at 38%.
- The NCPE review team has concerns that the uncertainty due to the single-armed evidence and immature survival data is not captured appropriately in the sensitivity analyses.

4. Budget impact of daratumumab (Darzalex®)

- The list price of daratumumab is €1,824 (400mg) and €456 (100mg). Assuming treatment duration of 4 months based on PFS from the pooled trials, the annual cost of daratumumab per patient, including rebates and VAT, is estimated as €86,024. The estimated cost of pomalidomide plus dexamethasone for 4 months of treatment is €41,708.
- The projected gross budget impact (including VAT and rebates), based on company estimates of market share is €3,522,692 (year 1), €5,032,418 (year 2), €3,522,692 (year 3), €3,019,451 (year 4) and €2,516,209 (year 5). This results in a cumulative budget impact of €17.6M over 5-years.
- The company also presented a net budget impact representing the gross budget impact when daratumumab is introduced minus the gross budget impact of continuing the current treatment pathway assuming daratumumab is not introduced. The cumulative net budget impact over 5-years is estimated at €12.2M.

5. Patient submissions

- No patient submissions were received in support of the application.

6. Conclusion

Following NCPE assessment of the company submission, daratumumab (Darzalex®) monotherapy is not considered to be cost-effective for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a protease inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.