Cost-effectiveness of daratumumab (Darzalex®) in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of daratumumab (Darzalex®). Following assessment of the Applicant's submission, the NCPE recommends that daratumumab (Darzalex®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Janssen) Health Technology Assessment 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 **November 2021**

Summary

In February 2021, Janssen submitted a dossier examining the clinical effectiveness, cost-effectiveness, and budget impact of daratumumab in combination with bortezomib, thalidomide and dexamethasone (dar+bor+thal+dex) for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT). The European Medicines Agency (EMA) granted a licence extension for daratumumab solution for infusion in combination with bor+thal+dex for this indication in January 2020. Daratumumab was designated an orphan medicinal product in July 2013 by the EMA. Orphan status was maintained in January 2020.

The recommended dose of daratumumab is 16mg/kg administered through intravenous (IV) infusion. The dosing schedule for dar+bor+thal+dex is made up of six 4-week treatment cycles. Cycles 1 to 4 are administered as induction therapy before treatment is stopped for the patient to receive high dose chemotherapy and ASCT. Cycles 5 and 6 are administered as consolidation therapy post-ASCT. Daratumumab is administered weekly in cycles 1 and 2 and then every second week for cycles 3 to 6. Bortezomib is administered subcutaneously (SC) or IV at a dose of 1.3mg/m^2 on days 1, 4, 8 and 11 in cycles 1 to 6. Thalidomide is administered orally at a dose of 100mg daily in cycles 1 to 6. Dexamethasone is administered orally at a dose of 40mg twice weekly in cycles 1 and 2, 40mg on days 1 and 2 and 20mg on days 8, 9, 15 and 16 of cycles 3 and 4, and 20mg on days 1, 2, 8, 9, 15 and 16 of cycles 5 and 6. In June 2020, a solution formulation of daratumumab for SC injection was granted marketing authorisation by the EMA. The recommended dose is 1,800mg SC; the dosing schedule is the same as that for the IV formulation. The current submission pertains to the IV formulation of daratumumab only. The Applicant is seeking reimbursement in the hospital setting. Daratumumab is a human monoclonal antibody that targets CD38.

Based on frequency of use in Ireland, bortezomib in combination with cyclophosphamide and dexamethasone (bor+cyclo+dex) and bortezomib in combination with lenalidomide and dexamethasone (bor+len+dex) were included as comparators in the cost-effectiveness analysis. Bortezomib in combination with thalidomide and dexamethasone (bor+thal+dex), although used less frequently in Ireland, is licensed in this setting, and was therefore also

included as a comparator. Bor+thal+dex provides the most rigorous comparison with dar+bor+thal+dex due to the availability of head-to-head trial data.

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

Direct comparative evidence for the effectiveness of dar+bor+thal+dex versus bor+thal+dex in patients with NDMM eligible for ASCT is available from the CASSIOPEIA phase III, open-label, multicentre, randomised controlled trial (RCT). CASSIOPEIA is a two-part study, comprising:

- Part 1, designed to compare the efficacy of dar+bor+thal+dex versus bor+thal+dex as induction and consolidation treatment before and after patients undergo ASCT. (The licence includes dar+bor+thal+dex as induction and consolidation treatment only).
- Part 2, in which patients who achieved a partial response or better at day 100 post-ASCT were re-randomised to receive daratumumab monotherapy as maintenance treatment or undergo observation, until disease progression or for a maximum of two-years.

Patients were randomised in a 1:1 ratio to receive dar+bor+thal+dex (n=543) or bor+thal+dex (n=542). The primary endpoint was proportion of patients with a stringent complete response (sCR) post-consolidation. Secondary endpoints included progression-free survival (PFS) and overall survival (OS) both from first randomisation, health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes.

The primary analysis provided the final analysis of post-consolidation sCR and interim analyses of PFS and OS (Part 1), with a median follow-up of 18.8 months. At the primary analysis, , 157 (29%) individuals receiving dar+bor+thal+dex and 110 (20%) individuals receiving bor+thal+dex had achieved a post-consolidation sCR (odds ratio 1.60, 95% CI 1.21 to 2.12). Median PFS was not reached in patients receiving dar+bor+thal+dex or bor+thal+dex; hazard ratio (HR) = 0.47 (95% CI 0.33 to 0.67). Median OS was not reached in either treatment arm; HR = 0.43 (95% CI 0.23 to 0.80)

The most recent data for PFS and OS, based on patients' original randomisation to dar+bor+thal+dex or bor+thal+dex, is available from the first interim analysis from Part 2 of CASSIOPEIA, with a median follow-up of 44.5 months. PFS was not reached in individuals receiving dar+bor+thal+dex, with a median PFS of 51.5 months in individuals receiving bor+thal+dex; HR = 0.58 (95% CI 0.47 to 0.72). Median OS was not reached in either treatment arm; HR= 0.54 (95% CI 0.37 to 0.79).

HRQoL scores indicated that daratumumab was not detrimental to HRQoL. The NCPE Review Group has concerns regarding the immaturity of the survival data, and that re-randomisation to Part 2 of the trial may introduce confounding into longer term survival outcomes.

In the absence of direct comparative evidence, an indirect treatment comparison was conducted via a matched adjusted indirect comparison (MAIC), using RCT evidence, to establish estimates of relative effectiveness of dar+bor+thal+dex compared to bor+cyclo+dex and bor+len+dex, for use in the cost-effectiveness model. Two RCTs were included in the MAIC with CASSIOPEIA: GMMG-MM5 (comparison with bor+cyclo+dex) and IFM 2009 (comparison with bor+len+dex). In general, the three trials had similar designs, comparable eligibility criteria, and sufficient overlap in most baseline characteristics to conduct a MAIC. Overall, the results indicate longer PFS and OS with dar+bor+thal+dex versus both bor+cyclo+dex and bor+len+dex. Equivalent PFS and OS is demonstrated with bor+thal+dex versus bor+cyclo+dex and bor+len+dex. The major limitation of the MAIC is the inability to adjust for differences in the maintenance therapies between the three trials (daratumumab monotherapy or observation in CASSIOPEIA and lenalidomide in GMMG-MM5 and IFM 2009), such that any analyses reflect the comparison of the overall treatment schema of the trials rather than a comparison of induction and consolidation therapies. There are also concerns regarding the inclusion of a second ASCT in the comparator trials and the immaturity of the included data. Any uncertainty in the results of the MAIC will translate into uncertainty in the cost-effectiveness model.

2. Safety of daratumumab (Darzalex®)

The safety population of the CASSIOPEIA trial included all patients who received at least one dose of study treatment. Results are presented for the induction/ASCT/consolidation period

of CASSIOPEIA. Median treatment duration was 8.9 months in individuals receiving dar+bor+thal+dex and 8.7 months in individuals receiving bor+thal+dex.

Treatment-emergent adverse events (TEAEs) were observed in 99.8% of individuals receiving dar+bor+thal+dex and 99.6% receiving bor+thal+dex. Grade 3 to 4 TEAEs were more common in individuals receiving dar+bor+thal+dex (80.6%) compared to those receiving bor+thal+dex (75.8%). The most reported grade 3 to 4 TEAEs in individuals receiving dar+bor+thal+dex were neutropenia (27.6% vs 14.7% in individuals receiving bor+thal+dex), lymphopenia (17.0% vs 9.7%), stomatitis (12.7% vs 16.4%), thrombocytopenia (11.0% vs 7.4%), peripheral sensory neuropathy (8.8% vs 8.6%) and febrile neutropenia (6.7% vs 5.2%). Serious adverse events occurring in at least 3% of individuals receiving either dar+bor+thal+dex or bor+thal+dex, respectively, were neutropenia (3.9% vs 1.5%), pneumonia (3.5% vs 1.7%), pyrexia (2.8% vs 4.3%) and pulmonary embolism (1.5% vs 3.7%).

3. Cost effectiveness of daratumumab (Darzalex®)

Methods

The cost-effectiveness of dar+bor+thal+dex was assessed using a three-state partitioned survival cost-utility model with a cycle length of 28 days and a life-time horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the progression-free (induction, ASCT, consolidation and maintenance) health state and receives active treatment with either dar+bor+thal+dex or one of the comparators. Individuals remain in the progression-free health state until they experience disease progression where they move to the post-progression health state, where individuals can receive up to two lines of subsequent treatment. Costs of disease management, utilities and risk of death all differ between the progression-free and post-progression health states. The partitioned survival model uses the “area under the curve” approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to clinical trial data.

Clinical data for dar+bor+thal+dex and the comparison with bor+thal+dex in the model base case were obtained from the CASSIOPEIA trial (44.5 month data-cut). The bor+cyclo+dex

and bor+len+dex comparisons were informed by the clinical evidence from the GMMG-MM5 and IFM 2009 trials, respectively. The key effectiveness inputs in the model were PFS, OS and time to treatment discontinuation (TTD). For the comparisons with bor+cyclo+dex and bor+len+dex, HRs from the MAIC were applied to reference curves from CASSIOPEIA for PFS and OS, with TTD modelled based on the median treatment duration in the GMMG-MM5 and IFM 2009 trials, respectively.

Utilities identified in the model included utilities associated with each treatment phase in the progression-free health state (i.e., induction, ASCT, consolidation, maintenance), and the post-progression health state. Utility decrements were included for TEAEs. The same utilities were used regardless of treatment regimen. The derivation of utilities for induction, consolidation, and maintenance in the progression-free health state and for the post-progression health state were derived from EQ-5D-5L data from CASSIOPEIA. EQ-5D-5L utilities were mapped to the EQ-5D-3L using the mapping function developed by van Hout et al. (2012). The utility for individuals undergoing ASCT was assumed to be the same as for the induction phase.

The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition, administration, concomitant medications, ASCT and TEAEs. Other healthcare resources were aggregated as health state-specific costs and included subsequent treatments, and costs of routine care and follow-up. A once-off end-of-life cost was applied. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested two main changes to the Applicant base case based on plausible and conservative alternative assumptions. These included the use of individual treatment curves for PFS and OS and the application of a treatment waning effect assuming no additional benefit five-years post-consolidation. The NCPE adjusted incremental cost-effectiveness ratios (ICERs) (Table 1) and the Applicant ICERs (Table 2) are shown.

Table 1: NCPE adjusted deterministic base case analysis*

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Dar+bor+thal+dex	340,822	7.90			
Bor+thal+dex	302,417	7.33	38,405	0.57	66,979
Bor+cyclo+dex	274,325	6.44	66,496	1.46	45,562
Bor+len+dex	274,023	6.51	66,799	1.39	48,150

Bor: bortezomib; **cyclo:** cyclophosphamide; **dar:** daratumumab; **dex:** dexamethasone; **ICER:** incremental cost effectiveness ratio; **QALY:** quality adjusted life year; **len:** lenalidomide; **thal:** thalidomide.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.
A commercial in confidence patient access scheme is currently in place for dar in combination with bor + dex, but not included in this analysis.

Table 2: Applicant deterministic base case analysis*

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Dar+bor+thal+dex	376,252	9.39			
Bor+thal+dex	301,547	7.28	74,705	2.12	35,319
Bor+cyclo+dex	273,523	6.40	102,729	2.99	34,300
Bor+len+dex	273,206	6.47	103,047	2.92	35,250

Bor: bortezomib; **cyclo:** cyclophosphamide; **dar:** daratumumab; **dex:** dexamethasone; **ICER:** incremental cost effectiveness ratio; **QALY:** quality adjusted life year; **len:** lenalidomide; **thal:** thalidomide.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.
A commercial in confidence patient access scheme is currently in place for dar in combination with bor + dex, but not included in this analysis.

The probability of dar+bor+thal+dex being cost-effective versus bor+thal+dex, bor+cyclo+dex and bor+len+dex was 0.5%, 0.8% and 0.1% respectively at thresholds of both €20,000 per QALY and €45,000 per QALY, using the NCPE adjusted base case.

Deterministic sensitivity analyses indicated that the NCPE adjusted base case was most sensitive to assumptions surrounding discount rate, time horizon, the choice of OS and PFS survival distributions, the MAIC reference curve, the proportion of patients receiving consolidation therapy, and subsequent treatments.

4. Budget impact of daratumumab (Darzalex®)

The price to wholesaler of daratumumab is €448 for a 5ml vial containing 100mg of daratumumab (20mg/ml) and €1,743 for a 20ml vial containing 400mg of daratumumab (20mg/ml). The average total cost per treatment course (induction and consolidation) for dar+bor+thal+dex, including all relevant fees, mark-ups and rebates is €98,058 (€121,356 including VAT).

Accounting for a full 12-months treatment in year 1, it was estimated that 31 individuals would be treated with dar+bor+thal+dex, increasing to 33 in year 5. The projected

cumulative five-year gross drug budget impact of dar+bor+thal+dex is €19.4 million including VAT and €15.7 million excluding VAT.

The net drug budget impact assumes that dar+bor+thal+dex will displace bor+cyclo+dex and bor+len+dex. The price of lenalidomide was assumed to be reduced by 50% to represent loss of market exclusivity in early 2022. Bor+thal+dex was not included due to declining use over recent years. The cumulative five-year net drug budget impact is estimated as €16.7 million including VAT and €13.4 million excluding VAT. An additional net budget impact is presented including costs for ASCT, maintenance treatment and second-line therapies. The cumulative net budget impact over five-years is estimated as €13.8 million including VAT and €10.9 million excluding VAT.

5. Patient Submissions.

No patient submissions were received in support of the application.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommend that daratumumab (Darzalex®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.