Cost-effectiveness of Daratumumab (Darzalex®) in Combination with Bortezomib and Dexamethasone for the Treatment of Adult Patients with Multiple Myeloma who have Received at Least One Prior Therapy

The NCPE has issued a recommendation regarding the cost-effectiveness of daratumumab combination (Darzalex®).
Following assessment of the applicant's submission, the NCPE recommends that daratumumab combination (Darzalex®) not be considered for reimbursement unless 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Janssen) economic dossier on the cost effectiveness of daratumumab combination (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 2019**

Summary

In April 2017 the EU Commission granted marketing authorisation for daratumumab in combination with lenalidomide and dexamethasone (DAR+LEN+DEX), or bortezomib and dexamethasone (DAR+BOR+DEX) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy. DAR was designated an orphan medicinal product on 17 July 2013 by the EMA. In September 2018, Janssen submitted a dossier examining the cost-effectiveness of DAR+BOR+DEX for the treatment of MM in patients who have received at least one prior therapy; information on DAR+LEN+DEX was not presented.

The recommended dose of DAR is 16mg/kg administered through intravenous (IV) infusion. DAR is administered every week for weeks 1-9, every 3 weeks for weeks 10 to 24 and every four weeks from week 25 until disease progression. BOR is administered sub-cutaneously (SC) at a dose of 1.3mg/m^2 on days 1, 4, 8, and 11 for eight 21-day cycle (cycles 1-8). DEX is administered orally at a dose of 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12, of the first eight BOR treatment cycles (i.e. total dose of 160mg per cycle). The Applicant is seeking reimbursement in the hospital setting. DAR is a human monoclonal antibody that targets CD38.

BOR+DEX, LEN+DEX, carfilzomib + dexamethasone (CAR+DEX), CAR+LEN+DEX and BOR+LEN+DEX were the chosen comparators in the cost-effectiveness analysis.

1. **Comparative effectiveness of DAR+BOR+DEX**

The only direct evidence available for the efficacy of DAR+BOR+DEX is from the multicentre, phase III, randomised, open-label, CASTOR trial comparing DAR+BOR+DEX (n=251) with BOR+DEX (n=247) in patients with relapsed/refractory (RR) MM who have received at least one prior therapy. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), time to disease progression (TTP), objective response rate (ORR), duration of response (DoR), minimal residual disease (MRD), safety and health-related quality of life (HRQoL) measures. The latest data-cut from the CASTOR trial is the IA3 interim analysis (20 December 2017), with a median follow-up of 26.9

months. Results are presented for the ITT population and for the sub-group of patients who had received one previous treatment (i.e. second-line patients).

For the ITT population the median PFS was 16.72 months (95% CI 13.14, 19.38) in the DAR+BOR+DEX arm and 7.06 months (95% CI 6.21, 7.66) in the BOR+DEX arm; HR = 0.32 (95% CI 0.25, 0.40). For the second-line population median PFS was 26.22 months (95% CI 21.19, NE) in the DAR+BOR+DEX arm and 7.92 months (95% CI 6.77, 9.03) in the BOR+DEX arm; HR = 0.23 (95% CI 0.16, 0.33). For the ITT population the median OS was not reached in the DAR+BOR+DEX arm and 31.18 months (95% CI 28.85, NE) in the BOR+DEX arm; HR = 0.77 (95% CI 0.57, 1.04). For the second-line population median OS was not reached in either arm; HR = 0.50 (95% CI 0.30, 0.84). HRQoL scores indicated similar patient reported QoL in both treatment arms. The NCPE review team has concerns regarding the immaturity of the OS data and potential confounding in OS due to subsequent treatments, resulting in uncertainty in the OS estimates. There are also concerns that bias may have been introduced into patient-reported and investigator-assessed outcomes, due to the open-label nature of the trial.

In the absence of direct comparative evidence, an indirect treatment comparison was conducted via a network meta-analysis (NMA), using randomised controlled trial (RCT) evidence, to establish estimates of relative effectiveness of DAR+BOR+DEX compared to LEN+DEX, CAR+DEX and CAR+LEN+DEX, for use in the economic model. The NMA included six RCTS; CASTOR (DAR+BOR+DEX vs. BOR+DEX), ENDEAVOR (CAR+DEX vs. BOR+DEX), APEX (BOR vs. DEX), MM-009 & MM-010 (LEN+DEX vs. DEX) and ASPIRE (CAR+LEN+DEX vs. LEN+DEX). In order to form a connected network, it was assumed that the relative efficacy of BOR vs. DEX in the APEX trial is the same as the relative efficacy of BOR+DEX vs. DEX. Whilst the NCPE review team has some concerns regarding the validity of this assumption, it is acknowledged that the approach taken to the NMA is appropriate given the limitations in the available evidence. The NCPE review team recommends that any conclusions derived from the NMA should be interpreted with caution due to the following limitations which will affect the robustness of the survival results: (i) potential confounding in OS due to immature data and/or cross-over; (ii) differences in median PFS across common-comparator arms in the trials, potentially caused by differences in patient populations; (iii) differences in dosing

schedules and treatment duration for common-comparator arms in the trials and (iv) differences in length of follow-up.

As BOR+LEN+DEX therapy in RRMM has not been evaluated in an RCT, the Applicant conducted two sensitivity analyses adding BOR+LEN+DEX to the NMA using data from observational studies. As this comparison is based on non-RCT data it is less reliable than the other comparisons derived from the NMA including RCT data only.

2. Safety of DAR+BOR+DEX

At median follow-up of 26.9 months, median duration of treatment was 13.37 months for the DAR+BOR+DEX arm and 5.22 months for the BOR+DEX arm. The safety population included all patients who had received at least one dose of study drug.

Adverse events (AEs) were generally similar across treatment groups. The most common grade 3–4 haematological AEs were thrombocytopenia (45.7% DAR+BOR+DEX; 32.9% BOR+DEX), anaemia (15.2% DAR+BOR+DEX; 16.0% BOR+DEX), neutropenia (13.6% DAR+BOR+DEX; 4.6% BOR+DEX) and lymphopenia (9.9% DAR+BOR+DEX; 2.5% BOR+DEX). The most common grade 3–4 non-haematological AEs in both treatment groups included pneumonia (10.3% DAR+BOR+DEX; 10.1% BOR+DEX), hypertension (6.6% DAR+BOR+DEX; 0.8% BOR+DEX), fatigue (4.9% DAR+BOR+DEX; 3.4% BOR+DEX) and peripheral sensory neuropathy (4.5% DAR+BOR+DEX; 6.8% BOR+DEX). Safety data from interim analysis 1 (IA1; median follow-up 7.4 months) reported infusion-related reactions (IRRs) in 45% of DAR patients, of which most were of grade 1 or 2 severity and occurred on day 1 of the first infusion.

3. Cost effectiveness of DAR+BOR+DEX

Methods

The cost-effectiveness model was a cost-utility partitioned survival model with a 40-year time horizon and cycle length of one week. The key effectiveness inputs in the model were PFS, OS and time to treatment discontinuation (TTD). Treatment effects and time-to-event data for DAR+BOR+DEX and BOR+DEX were informed by statistical analyses of patient-level data from the second-line population enrolled in the CASTOR trial. The relative treatment

effect for comparators was informed by the NMA. The NCPE review team considers that the ITT population from the CASTOR trial may be more reflective of the Irish clinical population than the second-line population and is therefore the appropriate patient population to include in the cost-effectiveness model. However, it is acknowledged that clinical preference in Ireland is to use triplet therapies as early in the disease course as possible i.e. second line.

The model simulates patients through three mutually exclusive health states; pre-progression, post-progression and death, directly capturing PFS and OS. Patients who are eligible for treatment entered the model, initiated treatment, and experienced an interval of PFS. Patients who experienced disease progression and did not die during the initial modelled line of treatment continued to the post-progression health state and could receive subsequent treatments. Patients could die at any time point in the model. Death is an absorbing state. Treatment status in both the pre-progression (trial treatment) and post-progression (subsequent treatment) states was also tracked. Costs and utilities were assigned to each health state and were applied according to the patients' disease progression status and type of treatment received. Utility values were derived from data for second-line patients from the CASTOR trial for the pre-progression health state. Due to a lack of data, a post-progression utility value was obtained from the literature. The same utilities were used in each health state regardless of treatment. A one-off utility decrement for AEs was applied at the start of treatment.

For the DAR+BOR+DEX vs. BOR+DEX comparison, survival and treatment discontinuation outcomes from CASTOR were extrapolated to the full time-horizon of the model. Separate parametric models were fitted to each treatment arm. Several distributions were assessed and the most appropriate was chosen. For PFS and TTD the same curve was used for both arms to maintain consistency. The Applicant considered that the distributions for DAR+BOR+DEX and BOR+DEX OS would differ due to the perceived minimal residual disease (MRD) advantage with DAR+BOR+DEX and its innovative mechanism of action. Therefore, different distributions were used for each treatment arm. The NCPE review team considers the justification for the use of separate distributions to be insufficient to warrant the use of different curves. There are also concerns regarding the long-term estimates of DAR+BOR+DEX OS with the chosen distribution. For the CAR+DEX, LEN+DEX and

CAR+LEN+DEX comparisons, comparative efficacy was based on estimates from the NMA including RCT evidence only. HRs for PFS and OS were applied to the reference curve of BOR+DEX from the CASTOR trial. A comparison of DAR+BOR+DEX vs. BOR+LEN+DEX was carried out as a sensitivity analysis and not included in the base case. Two methods were included to connect BOR+LEN+DEX to the NMA; via an unanchored MAIC and via the assumption that the clinical efficacy for BOR+LEN+DEX compared with CAR+LEN+DEX is the same as the difference between CAR+DEX and BOR+DEX observed in the ENDEAVOUR trial. As with the other comparisons HRs were applied to the BOR+DEX reference curve.

All relevant costs are included in the model. Costs were included for drug acquisition and administration, routine follow-up care, costs of unplanned events such as AEs and progression, and terminal care costs. Irish cost data were used where possible.

The NCPE review team identified several key issues and uncertainties with the economic model. The main issue being the use of the second-line population in preference to the ITT population. Analysis of the results of the NMA based on the ITT population suggest that this population may be associated with higher ICERs and therefore decreased cost-effectiveness compared to the second-line population. There are also concerns regarding the choice and application of distributions to extrapolate trial data and potential subsequent treatments. Overall the NCPE review team has concerns that the cost-effectiveness model is associated with a high degree of uncertainty, together with high ICERs for all comparisons using the NCPE preferred base case.

Results

Applicant base case

- The incremental cost due to treatment with DAR+BOR+DEX vs. BOR+DEX is €181,994 for a QALY gain of 2.08 resulting in an ICER of **€87,623** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. CAR+DEX is €45,367 for a QALY gain of 1.55 resulting in an ICER of **€29,297** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. LEN+DEX is €146,723 for a QALY gain of 1.95 resulting in an ICER of **€75,058** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. CAR+LEN+DEX is

€59,966 for a QALY gain of 1.56 resulting in an ICER of **€38,481** per QALY.

Due to uncertainty in the assumptions used in the economic model the NCPE suggested several changes based on plausible alternative assumptions. This gave the following results:

- The incremental cost due to treatment with DAR+BOR+DEX vs. BOR+DEX is €173,179 for a QALY gain of 1.40 resulting in an ICER of **€123,721** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. CAR+DEX is €35,794 for a QALY gain of 0.87 resulting in an ICER of **€41,084** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. LEN+DEX is €137,456 for a QALY gain of 1.28 resulting in an ICER of **€107,594** per QALY.
- The incremental cost due to treatment with DAR+BOR+DEX vs. CAR+LEN+DEX is €44,950 for a QALY gain of 0.88 resulting in an ICER of **€51,015** per QALY.

BOR+LEN+DEX comparison – applicant base case

- Based on the unadjusted MAIC, the incremental cost due to treatment with DAR+BOR+DEX vs. BOR+LEN+DEX is €82,880 for a QALY gain of 0.96 resulting in an ICER of **€86,496** per QALY.
- Based on the ENDEAVOR assumption, the incremental cost due to treatment with DAR+BOR+DEX vs. BOR+LEN+DEX is €136,016 for a QALY gain of 2.08 resulting in an ICER of **€65,322** per QALY.

Using the NCPE preferred assumptions as for the base case gave rise to the following results:

- Based on the unadjusted MAIC, the incremental cost due to treatment with DAR+BOR+DEX vs. BOR+LEN+DEX is €79,629 for a QALY gain of 0.28 resulting in an ICER of **€283,441** per QALY. It should be noted that this result is particularly uncertain due to small patient numbers.
- Based on the ENDEAVOR assumption, the incremental cost due to treatment with DAR+BOR+DEX vs. BOR+LEN+DEX is €130,551 for a QALY gain of 1.40 resulting in an ICER of **€92,920** per QALY.

Sensitivity analysis

The applicant presented a probabilistic sensitivity analysis (PSA) for each comparison, which gave the following ICERs:

- DAR+BOR+DEX vs. BOR+DEX = **€85,455** per QALY.
- DAR+BOR+DEX vs. CAR+DEX = **€14,790** per QALY.
- DAR+BOR+DEX vs. LEN+DEX = **€95,239** per QALY.
- DAR+BOR+DEX vs. CAR+LEN+DEX = **€46,424** per QALY.

The applicant presented the probability of being cost-effective at €20,000, €40,000 and €60,000 per QALY thresholds. At a willingness to pay threshold of €20,000 per QALY, BOR+DEX had the highest probability of being the most cost-effective treatment (89.4%) followed by LEN+DEX (10.4%), CAR+LEN+DEX (0.2%), DAR+BOR+DEX and CAR+DEX (both 0%). At a willingness to pay threshold of €40,000 per QALY the probabilities of each treatment being the most cost-effective treatment were, BOR+DEX (65.1%), LEN+DEX (27.9%), CAR+LEN+DEX (6.6%), CAR+DEX (0.4%) and DAR+BOR+DEX (0%). A PSA was not presented for the BOR+LEN+DEX comparison.

The applicant also presented a variety of scenario analyses and one-way sensitivity analyses. These analyses indicated that the model was most sensitive to assumptions and parameters relating to PFS, OS and discounting. No sensitivity analyses were presented for the BOR +LEN+DEX comparison.

4. Budget impact of DAR+BOR+DEX

The price to wholesaler is €456 for a 5ml vial containing 100mg of DAR (20mg/ml) and €1,824 for a 20ml vial containing 400mg of DAR (20mg/ml). The average annual cost per patient of DAR+BOR+DEX, including all relevant fees, mark-ups and rebates, is estimated as €111,365 and €104,969 for DAR alone.

Based on company estimates of market share, the applicant estimates that there will be 38 patients receiving DAR+BOR+DEX in year 1, rising to 81 in year 5. The projected gross budget impact including drug acquisition costs only for DAR+BOR+DEX is estimated as €4,320,945

(year 1), €8,743,480 (year 2), €10,289,434 (year 3), €9,836,161 (year 4) and €8,986,771 (year 5). This results in a cumulative gross budget impact of €42.2M over 5-years.

The applicant also presented a net drug budget impact representing the gross budget impact when DAR is introduced minus the gross budget impact of continuing the current treatment pathway for RRMM assuming DAR+BOR+DEX is not introduced. The cumulative net drug budget impact over 5-years is estimated as €16.4M.

An additional net budget impact is presented including costs associated with administration, subsequent treatment, AEs, monitoring and a one-off cost for terminal care. The cumulative net budget impact over 5-years is estimated as €11.8M.

5. State if any patient submissions were received, and name submitting organisations.

No patient submissions were received in support of the application.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that daratumumab combination (Darzalex®) not be considered for reimbursement unless 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.