NCPE Technical Summary

Daratumumab (Darzalex®)

HTA ID: 22039

September 2023

Applicant: Janssen Ireland

Daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

NCPE
National Centre for Pharmacoeconomics, Ireland

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®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Janssen Ireland) 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.

Summary

In January 2023, Janssen Ireland submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of daratumumab in combination with lenalidomide and dexamethasone (dar+len+dex) for the treatment of adults with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT). Reimbursement is sought under the Oncology Drugs Management System.

Daratumumab is an anti-CD38 monoclonal antibody which binds to the CD38 protein (a cell surface glycoprotein universally expressed on myeloma cells). Lenalidomide is an immunomodulatory imide drug. The combination of the two separate mechanisms of action of daratumumab and lenalidomide elicits signalling cascades and immune effector function engagement, leading to either myeloma cell death or inhibition of myeloma cells.

Daratumumab is available as a solution for subcutaneous injection (SC) with each vial containing 1,800mg of daratumumab. Daratumumab is administered at a dose of 1,800mg SC once a week from weeks one to eight, once every two weeks from weeks nine to 24 and once every four weeks from week 25 onwards. Lenalidomide is administered orally at a dose of 25mg once on days one to 21 of a 28-day treatment cycle. Dexamethasone is administered orally at a dose of 40mg (20mg for individuals over 75 years) once per week. All treatments are administered until disease progression or intolerance.

Current standard of care for patients with NDMM ineligible for ASCT includes len+dex, and several bortezomib-based treatment combinations i.e., bortezomib in combination with lenalidomide and dexamethasone (bor+len+dex), bortezomib in combination with melphalan and prednisone or prednisolone (bor+mel+pred) and bortezomib in combination with cyclophosphamide and dexamethasone (bor+cyclo+dex). These four comparators were considered appropriate.

1. Comparative effectiveness of daratumumab (Darzalex®)

The clinical evidence, supporting regulatory approval of dar+len+dex, comes from the ongoing, phase three, open-label, randomised control trial (RCT), MAIA, where dar+len+dex (n=368) is compared to len+dex (n=369). Adults who had NDMM and were not considered candidates for ASCT were eligible. Individuals in both trial arms were treated until disease progression or unacceptable toxicity.

The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall

survival (OS), minimal residual disease (MRD) negativity rate, overall response rate (ORR), health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. The October 2021 analysis, with a median follow-up of 64.5 months, is the most recent analysis that includes data for all endpoints. A further analysis for OS was conducted in October 2022, with a median follow-up of 73.6 months. The most recent data for each outcome were used to inform the cost-effectiveness model.

Median PFS was 61.9 months with dar+len+dex versus 34.4 months with len+dex; hazard ratio (HR) of 0.55 (95% confidence interval (CI) 0.45 to 0.67) (October 2021 analysis). Median OS was not reached for dar+len+dex and 64.1 months for len+dex; HR of 0.65 (95% CI 0.52 to 0.80) (October 2022 analysis).

Indirect comparative evidence

In the absence of direct head-to-head evidence, indirect comparative methods were required to inform the comparisons of dar+len+dex with bor+len+dex, bor+mel+pred and bor+cyclo+dex. The Review Group notes that a number of differences were observed between the baseline patient characteristics, design and procedures of the trials included in all indirect treatment comparisons. Thus, the outputs of all indirect analyses should be treated with caution. The Applicant did not use the indirect treatment comparison results in their cost-effectiveness model base cases. Instead, a naïve extrapolation was used for the comparison with bor+mel+pred and assumptions of comparative efficacy were implemented for the comparisons with bor+len+dex and bor+cyclo+dex.

A network meta-analysis (NMA), including len+dex as a common comparator, was performed to inform the comparison of dar+len+dex versus bor+len+dex, using the MAIA and SWOG S0777 trials. SWOG S0777 was an RCT comparing bor+len+dex versus len+dex in individuals with NDMM without intent for immediate ASCT. SW0777 included a mixed population of individuals who were transplant-eligible and individuals who were transplant-ineligible. Consequently, the subgroup of individuals aged over 65 was used as a proxy for patients who were transplant-ineligible. This aligns somewhat with transplant-ineligibility in the MAIA trial, where 99% of individuals were aged 65 or over. The results of the NMA estimated a PFS HR of 0.72 (95% CI 0.48 to 1.06) and an OS HR of 0.84 (95% CI 0.54 to 1.32).

An unanchored indirect treatment comparison was conducted to compare dar+len+dex versus bor+mel+pred using individual patient data from the MAIA and ALCYONE trials. ALCYONE is an RCT comparing dar+bor+mel+pred versus bor+mel+pred in individuals with transplant-ineligible NDMM.

The indirect comparison estimated a PFS HR of 0.28 (95% CI 0.22 to 0.35) and an OS HR of 0.68 (95% CI 0.51 to 0.90). The Review Group noted several key differences in the baseline characteristics between the MAIA and ALCYONE trials, which may lead to uncertainty in the robustness of the indirect comparison estimates.

Efficacy data for bor+cyclo+dex in the population with NDMM who are transplant-ineligible was only available from observational and real-world evidence studies. Based on naïve comparisons between these studies the Applicant considered that the efficacy of bor+cyclo+dex is likely to be similar to, or worse than, bor+mel+pred (dar+len+dex was not included as a treatment in the studies). The Review Group has concerns that the studies were not designed to compare different treatment regimens, as such any conclusions made on the relative treatment effects of bor+cyclo+dex and bor+mel+pred need to be treated with caution. The Applicant also conducted a matched-adjusted indirect comparison (MAIC) between bor+mel+pred (using the ALCYONE study) and bor+cyclo+dex (using the Jimenez-Zepeda *et al,* observational study). The following results were obtained; PFS HR of 1.24 (95% CI 1.0 to 1.55), OS HR of 1.14 (95% CI 0.83 to 1.56). The Review Group considers that the MAIC is possibly associated with biased estimates due to incomplete adjustment of prognostic factors and/or effect modifiers.

2. Safety of daratumumab (Darzalex®)

The safety analysis set, from the MAIA trial, included all randomised individuals who received any amount of study drug (n=364 for dar+len+dex and n=365 for len+dex). Results are presented for the October 2021 analysis, which was used to inform comparative clinical safety in the cost-effectiveness model.

Any grade treatment emergent adverse events (TEAEs) were reported in 100% of individuals receiving der+len+dex and 99.5% receiving len+dex. Grade 3 or above TEAEs were more common with dar+len+dex (95.9%) compared to len+dex (88.8%). The most reported grade 3 or above TEAES with dar+len+dex were neutropenia (54.1% versus 37.0% with len+dex), pneumonia (19.5% versus 10.7%), anaemia (17.0% versus 21.6%), lymphopenia (16.5% versus 11.2%), fatigue/asthenia (14.3% versus 9.6%), hypokalaemia (13.5% versus 10.4%), leukopenia (11.5% versus 6.3%), and cataract (11.0% versus 10.7%). The most common serious TEAEs were pneumonia (18.7% versus 10.7%) and pyrexia (5.5% versus 3.3%).

Although the safety profile of dar+len+dex is less favourable than len+dex, the additional toxicity

reflects the known safety profile of daratumumab. The majority of TEAEs are manageable, with no new safety findings observed.

3. Cost effectiveness of daratumumab (Darzalex®)

Methods

A cost-utility analysis, using a partitioned survival model, with cycle length of four weeks and a lifetime horizon, was submitted. A half cycle correction was applied. The model included three mutually exclusive health states: progression-free, progressed disease and death. Standard parametric models were used to extrapolate PFS and OS data from the MAIA trial for dar+len+dex and len+dex, and from the ALCYONE trial for bor+mel+pred. All treatment arms were extrapolated separately. Bor+len+dex was modelled as clinically equivalent to len+dex due to the absence of a statistically significant difference between the two treatments in the SWOG S0777 trial, for the subgroup of patients aged over 65. The Review Group notes that the SWOG S0777 trial was not powered to identify differences in subgroup analyses and that a statistically significant difference was observed in the ITT population for both PFS and OS. Based on consideration of the observational data for bor+cyclo+dex, clinical equivalence was assumed with bor+mel+pred.

Utility data were derived from EQ-5D-5L data, from the MAIA trial, mapped to EQ-5D-3L. Non-treatment-specific utility values were applied in the progression-free and progressed disease health states. Utility decrements were included for TEAEs and increasing age.

Direct medical costs were included for drug acquisition (including administration), disease management, subsequent treatment, routine care and monitoring, end-of-life care and the management of TEAEs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group made several changes to the Applicant base case based on plausible alternative assumptions. These included using a consistent distribution for extrapolation across all treatment arms i.e., PFS (Weibull), OS (Gompertz), and time-to-treatment discontinuation (TTD) (generalised gamma), using results from the NMA for the comparison with bor+len+dex in preference to the assumption of equivalent clinical efficacy with len+dex, and using Irish clinical opinion to inform resource use and subsequent treatment distribution estimates. The Applicant incremental cost-effectiveness ratios (ICER) and the NCPE-adjusted ICERs are shown in Table 1.

Table 1: Incremental cost -effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case					
Dar+len+dex	536,754	4.89			
Len+dex	279,091	3.37	257,663	1.52	169,634
Bor+len+dex	283,069	3.38	253,685	1.51	167,526
Bor+mel+pred	233,542	2.62	303,212	2.28	133,226
Bor+cyclo+dex	221,376	2.51	315,378	2.38	132,360
NCPE-adjusted base case					
Dar+len+dex	589,866	4.77	-	-	-
Len+dex	297,975	3.37	291,891	1.40	208,803
Bor+len+dex	325,976	3.86	263,890	0.91	290,725
Bor+mel+pred	259,091	2.62	330,775	2.15	153,709
Bor+cyclo+dex	244,994	2.51	344,872	2.26	152,681

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

Sensitivity analysis

Dar+len+dex had a 0% probability of being the most cost-effective treatment at both the €20,000 per QALY and €45,000 per QALY thresholds, for the Applicant and NCPE-adjusted base case.

Sensitivity analyses indicated that the main drivers of cost-effectiveness in both the Applicant and NCPE-adjusted base case were related to drug acquisition costs for all treatments, the distribution chosen for OS data extrapolation, and the distribution selected for the extrapolation of TTD in the dar+len+dex arm. The HR from the NMA was also influential in the NCPE-adjusted base case for the comparison with bor+len+dex.

4. Budget impact of daratumumab (Darzalex®)

The price-to-wholesaler of daratumumab is €5,346.05 for a 1,800mg vial, €2,183.20 for 21 x 25mg capsules of lenalidomide and €12.71 for 100 x 2mg tablets of dexamethasone. The total cost per patient per treatment course for dar+len+dex (assuming 100% dose intensity and mean treatment duration, informed by the MAIA trial, of 42.09 months) is €452,520 (€383,966 excluding VAT), including relevant fees, mark ups and rebates.

The Applicant used several sources to inform the eligible patient estimates. These included National Cancer Registry Ireland (NCRI) data, and clinical opinion. The Applicant assumed an initial market share for dar+len+dex of 40%, increasing to 50% in year five. Overall, the Applicant estimated that 60 individuals with NDMM who are ineligible for ASCT would be treated with dar+len+dex in year one, rising to 82 in year five. The Applicant also presented a net drug-budget impact assuming dar+len+dex will displace len+dex, bor+len+dex, bor+mel+pred and bor+cyclo+dex.

The Applicant estimated the cumulative five-year gross drug budget impact for dar+len+dex to be €130.18 million (€110.15 million excluding VAT). The cumulative five-year net drug budget impact for dar+len+dex was estimated to be €119.78 million (€100.10 million excluding VAT).

5. Patient Organisation Submission

A patient organisation submission, from Multiple Myeloma Ireland (MMI), was received during the course of the assessment. This will be provided to the HSE.

6. Conclusion

The NCPE recommends daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

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