Cost-effectiveness of daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of AL amyloidosis. 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. 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 Health Service Executive (HSE) asked the NCPE to carry out an appraisal of the Applicant's (Janssen Sciences Ireland) Health Technology Assessment on 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 drugs for cancer 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 **December 2022**

Summary

In April 2022, Janssen Sciences Ireland submitted a dossier of the clinical effectiveness, cost effectiveness and potential budget impact of DVCd (daratumumab (Darzalex®) in combination with bortezomib, cyclophosphamide and dexamethasone) for the treatment of newly diagnosed AL amyloidosis. The Applicant is seeking reimbursement for daratumumab as part of this regimen for the treatment of newly diagnosed AL amyloidosis on the Oncology Drugs Management System (ODMS). Daratumumab, as monotherapy and in combination, is already reimbursed through the ODMS for a number of multiple myeloma indications.

AL amyloidosis is a rare and incurable malignant plasma cell disorder, which results in the formation of amyloid fibrils that deposit in tissues and organs throughout the body. This results in life-threatening organ dysfunction; the heart and the kidneys are most commonly affected. The annual incidence of AL amyloidosis internationally is approximately three to 12 cases per million persons. The median age at diagnosis is 64 years. Nearly 60% of patients diagnosed with AL amyloidosis are male.

Daratumumab is an anti-CD38 monoclonal antibody which binds to CD38 proteins expressed on the surface of clonal plasma cells. This reduces native light chain production leading to reduced deposition of amyloid on organs. Daratumumab is available as a solution for subcutaneous (SC) injection 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 inclusive and then once every two weeks from weeks nine to 24 inclusive. Up until week 24 inclusive (i.e. six 28-day cycles) daratumumab is administered in combination with VCd (bortezomib, cyclophosphamide and dexamethasone). From week 25 onwards, daratumumab monotherapy can be continued every four weeks until disease progression or unacceptable toxicity, as per the Summary of Product Characteristics (SmPC).
Current standard of care for patients with AL amyloidosis is VCd. VCd treatment consists of the following drugs administered once a week, for a maximum of six 28-day cycles: bortezomib 1.3mg/m^2 SC, cyclophosphamide 300mg/m^2 either orally or intravenously (IV) and dexamethasone 40mg orally.

1. Comparative effectiveness of daratumumab

The clinical evidence, supporting regulatory approval of daratumumab, comes from the ongoing, phase three, open-label, randomised control trial (RCT), ANDROMEDA, where DVCd (n=195) followed by daratumumab monotherapy is compared to VCd (n=193). Adult patients who had histopathologically confirmed AL amyloidosis with organ involvement and had not received prior therapy were eligible. The primary endpoint was independently assessed overall complete haematologic response (CHR) rate. This is a surrogate endpoint, considered appropriate by the Committee for Human and Medicinal Products (CHMP) for regulatory purposes. Major-organ deterioration progression-free survival (MOD-PFS) and overall survival (OS) were secondary endpoints. The cumulative interim efficacy and safety was evaluated when at least 180 patients had been treated for six 28-day cycles (IA1 analysis). Baseline characteristics were generally well balanced across arms. The IA1 analysis had a median follow-up of 11.4 months. The Applicant also provided results from an 18-month landmark analysis; this analysis was not pre-specified. Key efficacy results are presented in Table 1.

Table 1 Clinical efficacy results from the primary (IA1) interim analysis and the 18-month landmark analysis (where available) from ANDROMEDA.

	IA1 interim analysis		**18-month landmark analysis**	
	DVCd (n=195)	**VCd (n=193)**	**DVCd (n=195)**	**VCd (n=193)**
Overall best confirmed haematological response rate % (95% CI)				
Primary endpoint: CHR°	53.3 (46.1, 60.5)	18.1 (13.0, 24.3)	59.5 (52.2, 66.4)	19.2 (13.9, 25.4)
VGPR	25.1 (19.2, 31.8)	31.1 (24.6, 38.1)	19.5 (14.2, 25.8)	31.1 (24.6, 38.1)
PR	13.3 (8.9, 18.9)	27.5 (21.3, 34.3)	12.8 (8.5, 18.3)	26.9 (20.8, 33.8)
NR	4.1 (1.8, 7.9)	19.7 (14.3, 26.0)	4.1 (1.8, 7.9)	19.2 (13.9, 25.4)
Key secondary endpoints				
Median MOD-PFS^	NR	NR	NR (NR, NR)	NR (NR, NR)
OS: Number of OS events	27 (13.8%)	29 (15%)	NA	NA
CHR at 6 months	49.7%	14%	50.3%	14%
CHR at 12 months¥	28.2%	7.3%	47.7%	12.4%
CHR at 18 months	NA	NA	50.3%	11.9%

NR: not reached; **NA:** not available; **CI:** confidence interval **CHR**: complete haematologic response; **VGPR**: very good partial response; **PR**: partial response; **NR**: no response; **MOD-PFS**: major organ deterioration progression-free survival

°Odds ratios of CHR (DVCd vs VCd) = 5.13 (95% CI 3.22 to 8.16); p <0.001 (IA1 analysis) and 6.03 (95% CI 3.80 to 9.58); p <0.0001 (18-month landmark analysis).

^Hazard ratio of 0.58 (0.36 to 0.93), p value of 0.0211.

¥ Perceived decline in the CHR between months 6 and 12 actually due to some patients not reaching 12 months follow-up at the IA1 analysis.

The CHMP commented that MOD-PFS is not a standard endpoint in AL amyloidosis. The final analysis for MOD-PFS will take place when approximately 200 MOD-PFS events have been observed. As such, the data are immature with only 43.5% of the 200 planned MOD-PFS events at the time of the IA1 analysis. Similarly, OS data are immature. The Applicant anticipates that the next pre-specified interim analysis of MOD-PFS and OS data will take place in quarter 1 2024. Health-related quality of life (HRQoL) data were collected from both arms up to cycle six inclusive, which indicated similar results for both arms. However, at cycle five, the VCd arm demonstrated a lower mean utility score before returning to a similar value as the DVCd arm at cycle six.

The Review Group highlighted a number of concerns with the clinical trial evidence from ANDROMEDA including: the trial was open-label, the immaturity of MOD-PFS and OS data, no evidence that the improvement in CHR with the addition of daratumumab is associated with an improvement in long-term outcomes such as OS, exclusion of patients with Stage 3B cardiac disease (advanced cardiac disease) at baseline and uncertainty regarding the optimal duration of daratumumab monotherapy. In the trial, patients in the DVCd arm could receive daratumumab for up to 24 treatment cycles. The circumstances in which continuation of daratumumab monotherapy may be beneficial and the most efficient treatment duration are unknowns. It could be reasonable to consider how this might be addressed through a randomisation of patients to different durations of treatment to support decision making for this treatment decision.

2. Safety of daratumumab

The safety profile of DVCd is informed by the ANDROMEDA safety analysis set which includes patients in the safety run-in set and randomised patients who received at least one administration of any study drug (n=381). As of the latest available data-cut (13 May 2021), 17.6% of patients in the DVCd arm had died, and 23.9% of patients in the VCd arm had died. More patients in the DVCd arm had died due to treatment-emergent adverse events (13.5%) compared with the VCd arm (8%). Fewer patients died from progression in the DVCd arm (2.1% vs. 6.9%). The cause of death due to TEAEs were not available for this data-cut according to the Applicant. However, data available from the 12-month landmark analysis indicated that cardiac disorders were the primary cause of death in both arms.

The CHMP concluded that the safety profile of daratumumab, in combination or as monotherapy, in AL amyloidosis is similar to the safety profile associated with daratumumab for multiple myeloma. The CHMP stated that there are no new safety findings, no new adverse drug reactions nor any new major concerns. However, further studies are being conducted to further characterise cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with SC daratumumab.

3. Cost effectiveness of daratumumab

The Applicant conducted a cost-utility analysis using a hybrid decision tree-Markov model developed in Microsoft Excel®. The population modelled comprised the intention-to-treat (ITT) population from ANDROMEDA. The licensed population includes all patients with newly diagnosed AL amyloidosis, including patients with advanced cardiac disease. The ANDROMEDA trial excluded patients with advanced cardiac disease (Stage 3B) at screening, although eight patients (2.1%) had progressed to Stage 3B disease at first study dose administration and were included in efficacy analyses. Clinical opinion indicates that patients with Stage 3B disease comprise 20% to 25% of patients diagnosed with AL amyloidosis in Ireland. Some cardiac involvement is anticipated in up to 50% of all patients. The Review Group consider that the trial population may not be generalisable to the population with AL amyloidosis in Ireland.

Treatment effectiveness is modelled through the depth of haematologic response achieved. The assumption is that deeper haematologic responses are associated with improved outcomes, including HRQoL and OS. Data from the 12-month landmark analysis of the ANDROMEDA trial were used to inform haematologic response distribution over six months within the decision tree. In the base case, patients exit the decision tree at six months. Haematologic response upon exit from the decision tree is used to determine the haematologic response pathway that patients enter in the Markov component: complete response (CR), very good partial response (VGPR) or partial response/no response (PR/NR). Data from the post-hoc 18-month landmark analysis indicate consistency in the CHR rate between six and 18 months. However, it is unclear if haematologic response is maintained beyond 18 months and over the life time horizon (35 years). Health-state transitions within each haematologic response pathway are informed by individual patient data from the

ANDROMEDA trial and are assumed to be constant over time (for each haematological response pathway).

Due to the immaturity of ANDROMEDA survival data, OS is informed by an external data source. In the base case, data from the EMN23 study (of patients with AL amyloidosis from 10 European countries diagnosed after 2010 (n=3,065)) is used to inform OS extrapolations. The EMN23 study population comprises 16% of people with Stage 3B cardiac disease. Alternative sources of OS data were available; the Review Group considered OS data from the UK study, ALchemy (n=1,194) co-ordinated by the National Amyloidosis Centre to also be informative for decision-making. Results of scenario analyses involving the ALchemy dataset are considered relevant for decision-making by the Review Group.

Patients who receive DVCd in the model are assumed to receive daratumumab for 18 x 28-day cycles, based on the mean duration of daratumumab therapy in ANDROMEDA. The Review Group highlight this may underestimate the cost of daratumumab treatment, in Irish clinical practice, as there is no stopping rule in the SmPC.

The Applicant updated their base case analysis in response to queries or comments made by the Review Group at preliminary review. Deterministic results of the Applicant's base case analysis are presented in Table 2.

Table 2 Deterministic results of the Applicant (updated) base case incremental cost effectiveness analysis

Treatment	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€/QALY)
DVCd	231,261	4.88	111,357	1.66	67,248
VCd	119,904	3.22	-	-	-

DVCd: daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone; **VCd**: bortezomib in combination with cyclophosphamide and dexamethasone; **QALYs**: quality adjusted life years; **ICER**: incremental cost-effectiveness ratio
Note: Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

The Review Group note model structural uncertainties, that cannot be overcome through scenario or sensitivity analyses including: patients remain in the same haematologic response pathway, based on haematologic response achieved after six months, for life; a surrogate outcome is used to inform effectiveness and HRQoL; the timepoint at which haematologic response is measured to inform stratification for OS extrapolations; the use of non-randomised observational data to inform OS extrapolations; the grouping of partial and non-responders into the same haematologic response pathway; the duration of daratumumab monotherapy. Given the sparsity of data, it was not possible to inform a NCPE-adjusted base case. However, the Review Group consider a number of alternative

assumptions to be equally as plausible as those used by the Applicant. Reflecting this, the Review Group report a range of plausible deterministic ICERs, from €66,254/QALY to €95,420/QALY.

The Applicant conducted a probabilistic sensitivity analysis, using 5,000 iterations, which resulted in a mean ICER of €70,764/QALY. The probability of DVCd being cost-effective is 0% at both willingness to pay thresholds of €20,000/QALY and €45,000/QALY.

4. Budget impact of daratumumab

Daratumumab is available as a 1,800mg solution for SC injection and the price to wholesaler of one vial is €5,346.05 excluding VAT. The Applicant assumes that patients will receive DVCd for six 28-day cycles and daratumumab monotherapy for a further 12 x 28-day cycles (based on the mean duration of daratumumab therapy in ANDROMEDA). In year one, the per-patient treatment cost of DVCd is estimated to be €161,517 including VAT (€129,486 excluding VAT) and the cost in year two is estimated to be €24,645 including VAT (€19,726 excluding VAT). The Applicant estimates the annual number of incident patients, newly diagnosed with AL amyloidosis, in Ireland in 2022 to be 36, rising to 38 in 2026. The Applicant assumes that DVCd will have annual market share of 72.5% over the next five years. Clinical opinion, to the Applicant and the Review Group, indicated that, if patients are eligible for VCd, they will likely receive daratumumab. Therefore, the Review Group consider the number of patients estimated to be treated with DVCd and the budget impact to be potentially underestimated.

The five-year cumulative gross drug budget impact of DVCd is estimated to be €24.04 million, including VAT. The five-year net drug budget impact of DVCd is estimated to be €22.06 million, including VAT. In a further analysis of the potential healthcare budget impact (not reported here), the Applicant has projected that DVCd will be associated with cost offsets in other areas of the healthcare budget, mainly related to administration and treatment costs of subsequent therapies. The Review Group consider any potential cost offsets in the healthcare budget to be highly uncertain.

5. Conclusion

The NCPE recommends that daratumumab 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.