NCPE Technical Summary

Carfilzomib (Kyprolis®)

HTA ID: 20054

July 2024

Applicant: Amgen Ireland Limited

Carfilzomib in combination with daratumumab and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of carfilzomib (Kyprolis®) in combination with daratumumab and dexamethasone.

Following assessment of the Applicant's submission, the NCPE recommends that carfilzomib (Kyprolis®) not be considered for reimbursement, for this indication *.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Amgen Ireland Limited) Health Technology Assessment of carfilzomib (Kyprolis®). 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 July 2023, Amgen Ireland Limited submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of carfilzomib (Kyprolis®) in combination with daratumumab and dexamethasone (car+dar+dex) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy. Amgen Ireland Limited are seeking reimbursement of carfilzomib on the Oncology Drug Management Scheme.

Carfilzomib is a selective proteasome inhibitor that irreversibly binds the proteasome, eliciting antimyeloma activity. Daratumumab is an anti-CD38 monoclonal antibody which exerts antimyeloma effects through immune-mediated, and immunoregulatory actions. The combination of the two separate mechanisms of action of carfilzomib and daratumumab promotes inhibition and death of myeloma cells.

The dosing schedule for car+dar+dex is described in Table 1.

Table 1: Dosing schedule for carfilzomib in combination with daratumumab and dexamethasone

Treatment	Dosing schedule (28-day treatment cycle)
Carfilzomib	IV administration on days 1, 2, 8, 9, 15 & 16. 20mg/m^2 on days 1 & 2 of cycle one, 56mg/m^2 thereafter, until disease progression.
Daratumumab*	IV administration of 16mg/kg^2 once every week for cycles 1 & 2, then once every 2 weeks for cycles 3 to 6 and once every 4 weeks from cycle 7 until disease progression.
Dexamethasone	40mg orally once every week until disease progression (20mg once every week for patients >75 years)

IV: intravenous; **SC:** subcutaneous
* Daratumumab is also available as a SC injection. 1800mg is administered using the same dosing schedule as described above. The clinical trial evidence for the current indication is based on the IV infusion. It is expected that patients will receive the SC injection in clinical practice. Both formulations are considered to exhibit equivalent safety and efficacy.

The Applicant anticipates that car+dar+dex will be used according to its licensed population i.e. in patients who have received at least one prior therapy for MM. In line with current standard of care in Ireland, the proposed comparators are carfilzomib in combination with dexamethasone (car+dex), daratumumab in combination with bortezomib and dexamethasone (dar+bor+dex), and pomalidomide in combination with bortezomib and dexamethasone (pom+bor+dex). Car+dex provides the most rigorous comparison with car+dar+dex due to the availability of head-to-head trial data.

As car+dar+dex is lenalidomide-sparing, the Applicant anticipates that it will predominantly be used in patients who have previously received lenalidomide, and as such lenalidomide-containing comparators were not considered. The patient population in the HTA base case included all patients regardless of prior therapies received, as per the licensed indication. A sub-group analysis was provided including only patients from the pivotal CANDOR trial who had previously received lenalidomide.

1. Comparative effectiveness of carfilzomib (Kyprolis®)

The clinical evidence, supporting regulatory approval of car+dar+dex, comes from the completed CANDOR trial. CANDOR is a phase III, open-label, randomised controlled trial (RCT) designed to evaluate the safety and efficacy of car+dar+dex (n=312) versus car+dex (n=154). Eligible participants were adults with relapsed or progressive MM, who had received at least one but no more than three prior lines of therapy for MM, with 42% of patients having received prior lenalidomide therapy. Treatment was continued until disease progression or unacceptable toxicity, up to a maximum of five years. The primary endpoint was progression-free survival (PFS), with overall survival (OS) measured as a key secondary endpoint.

Results from the July 2019 data-cut (median follow-up 17 months) include the primary PFS analysis, and provide the clinical basis supporting regulatory approval. Results from the June 2022 data-cut (median follow-up 50 months) provided the final analysis for OS. At the final analysis median PFS was 27.4 months in patients receiving car+dar+dex and 15.3 months in those receiving car+dex; hazard ratio (HR) of 0.63 (95% CI 0.49 to 0.81). Median OS was 50.8 months in patients receiving car+dar+dex and 43.6 months in those receiving car+dex; HR of 0.78 (95% CI 0.60 to 1.03). The Review Group has concerns that the lack of a statistically significant improvement in OS, may indicate that the PFS gains may not translate to gains in OS.

Indirect comparative evidence

In the absence of direct head-to-head evidence, indirect comparative methods were required to inform the comparisons of car+dar+dex with dar+bor+dex and pom+bor+dex. Although, a network of evidence could be constructed connecting car+dar+dex to dar+bor+dex and pom+bor+dex, the Applicant considered differences in the administration

schedule of the common comparator and imbalances in baseline characteristics across studies sufficient to preclude the construction of a network meta-analysis (NMA). Instead the Applicant conducted unanchored matched adjusted indirect comparisons (MAICs).

For the comparison of car+dar+dex and dar+bor+dex a MAIC was conducted using data from the CANDOR and CASTOR trials. CASTOR was an RCT comparing dar+bor+dex and bor+dex, which excluded patients who were refractory to proteasome inhibitors. To balance the patient populations between the CANDOR and CASTOR trials, the subgroup of patients who were not proteasome-inhibitor refractory were included from CASTOR. The results of the MAIC estimated a PFS HR of 0.67 (95% CI 0.53 to 0.85) and OS HR of 0.96 (95% CI 0.74 to 1.25).

The MAIC for the comparison of car+dar+dex and pom+bor+dex was informed by the CANDOR and OPTIMISSM trials. OPTIMISMM was an RCT comparing pom+bor+dex versus bor+dex in individuals, with relapsed or refractory MM, who had previously received lenalidomide. As such, the subgroup who had previously received lenalidomide were included from the CANDOR trial. The results of the MAIC estimated a PFS HR of 0.59 (95% CI 0.43 to 0.80) and an OS HR of 0.78 (0.56 to 1.12).

Separate time-dependent HRs were also calculated for both comparisons. Car+dar+dex was associated with a statistically significant benefit in PFS compared with both dar+bor+dex and pom+bor+dex from 24-weeks of follow-up onwards , with similar efficacy observed between treatments up to 24-weeks. OS was similar for car+dar+dex and both dar+bor+dex and pom+bor+dex, with a trend towards improved OS of car+dar+dex from 24-weeks.

The Review Group note that the outputs of unanchored MAICs are inherently uncertain due to the potential existence of unreported or unobserved confounding factors that cannot be adjusted for, breaking of randomisation, and smaller effective sample sizes. The substantial differences in population characteristics between the trials included here are a further source of uncertainty. Overall, the MAIC is associated with a high degree of uncertainty which will translate into uncertainty in decision making using the MAIC as a primary source for comparative effectiveness.

2. Safety of carfilzomib (Kyprolis®)

Overall, the safety data from CANDOR were consistent with the known safety profile of the individual drugs. Results are presented for the final analysis, which was used to inform comparative clinical safety in the cost-effectiveness model.

Any grade treatment emergent adverse events (TEAEs) were reported in 99.4% of individuals receiving car+dar+dex and 97.4% receiving car+dex. Grade 3 or above TEAEs were more common with car+dar+dex (88.6%) compared to car+dex (78.4%). The most reported Grade 3 or above TEAEs with car+dar+dex were thrombocytopenia (24.7% versus 16.3% with car+dex), hypertension (23.4% versus 17.6%), pneumonia (18.5% versus 9.2%), anaemia (17.5% versus 16.3%), and neutropenia (10.1% versus 6.5%).

3. Cost effectiveness of carfilzomib (Kyprolis®)

Methods

A cost-utility analysis, using a partitioned survival model, with cycle length of four-weeks (28 days) and a lifetime horizon, was submitted. A half cycle correction was applied. The model included three mutually exclusive health states: Progression-Free (PF), Post-Progression (PP) and Death. Standard parametric models were used to extrapolate PFS and OS data from the CANDOR trial for car+dar+dex and car+dex. Treatment arms were extrapolated separately. Time-dependent HRs, obtained from the MAIC analyses, were applied to the survival functions for PFS associated with car+dar+dex, for the comparisons with dar+bor+dex and pom+bor+dex, and to the survival functions for OS associated with car+dex for the comparison with dar+bor+dex. Due to uncertainty with the OS HR from the MAIC comparing car+dar+dex and pom+bor+dex, HRs were generated from a meta-regression of the relationship between PFS and OS, based on data from 17 RCTs.

Utility for all health states were informed by the CANDOR trial. Disutilities for TEAEs were also included.

Direct medical costs were included for drug acquisition (including administration), disease management, and subsequent treatments. A once-off end-of-life cost was applied. Irish costs were used where available.

Results

In the base case, the Applicant selected differing parametric models to extrapolate PFS in the car+dar+dex and car+dex arms. The Review Group selected the same distributions for each arm in an NCPE-adjusted base case. No changes were made to the Applicant base case for the comparisons with dar+bor+dex and pom+bor+dex. The results of the Applicant's base case, and the NCPE-adjusted, deterministic cost-effectiveness analyses are presented in Table 2. Sub-group analyses, including patients who had received previous treatment with lenalidomide only from CANDOR, are presented in Table 3. The Review Group notes that the results of this sub-group analysis are associated with a higher degree of uncertainty than the base case.

Table 2: Incremental cost-effectiveness results (licensed population)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analyses[a]					
Car+dar+dex	494,757	4.11	-	-	-
Car+dex	404,088	3.56	90,669	0.55	164,615
Dar+bor+dex	238,412	3.64	256,345	0.47	548,096
Pom+bor+dex	194,991	3.43	299,766	0.68	443,936
NCPE-adjusted analyses[b]					
Car+dar+dex	494,757	4.11	-	-	-
Car+dex	400,606	3.56	94,151	0.55	170,429

Bor: bortezomib; **car:** carfilzomib; **dar:** daratumumab; **dex:** dexamethasone; **ICER:** incremental cost-effectiveness ratio; **pom:** pomalidomide; **QALY:** quality adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations: vs car+dex = €167,740/QALY, vs dar+bor+dex = €538,857/QALY, vs pom+bor+dex = €439,373/QALY.

[b] Corresponding probabilistic ICER using 1,000 iterations: vs car+dex = €169,459/QALY.

Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Table 3: Incremental cost-effectiveness results sub-group analysis (previous lenalidomide treated population)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analyses[a]					
Car+dar+dex	513,463	3.91	-	-	-
Car+dex	326,814	3.28	186,649	0.63	297,001
Dar+bor+dex	195,392	3.34	318,071	0.58	552,922
Pom+bor+dex	182,859	3.03	330,604	0.88	376,114
NCPE-adjusted analyses[b]					
Car+dar+dex	513,463	3.91	-	-	-
Car+dex	274,400	3.27	239,063	0.65	368,792

Bor: bortezomib; **car:** carfilzomib; **dar:** daratumumab; **dex:** dexamethasone; **ICER:** incremental cost-effectiveness ratio; **pom:** pomalidomide; **QALY:** quality adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations: vs car+dex = €294,968/QALY, vs dar+bor+dex = €567,443/QALY, vs pom+bor+dex = €385,978/QALY.

[b] Corresponding probabilistic ICER using 1,000 iterations: vs car+dex = €369,277/QALY.

Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

Mean probabilistic ICERs were aligned with the respective deterministic ICERs. Sensitivity

analyses indicated that the main drivers of cost-effectiveness, in the Applicant base case, were assumptions surrounding OS extrapolation, including choice of survival distribution and HRs used.

An analysis of the price-ICER relationship was conducted which indicated that car+dar+dex could not achieve cost-effectiveness at any discount. This is due to the very high incremental cost of this combination treatment and small incremental benefit relative to comparators.

4. Budget impact of carfilzomib (Kyprolis®)

The price-to-wholesaler of carfilzomib is €194.42 for a 10mg vial, €585.54 for a 30mg vial and €1,154.02 for a 60 mg vial. The price-to-wholesaler of daratumumab is €446.85 and €1,739.70 for 100mg and 400mg vials, respectively. The price-to-wholesaler of dexamethasone is €12.71 for 100 x 2mg tablets. The total cost per patient per treatment course for car+dar+dex (assuming 100% dose intensity) is about €424,538 (€377,969 excluding VAT), including all 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, the published literature, and clinical opinion. Many of the inputs are uncertain and there is therefore considerable uncertainty associated with budget impact estimates. The Applicant estimated an initial market share of 5% in Year one increasing to 25% in Year five. Overall, the Applicant estimated eight individuals would be treated with car+dar+dex in Year one, rising to 44 in Year five. The Applicant also presented a net drug budget impact assuming car+dar+dex will displace car+dex, dar+bor+dex and pom+bor+dex. Based on the Applicant's assumptions, the five-year cumulative gross budget impact for car+dar+dex was estimated to be €50.03 million (€44.29 million excluding VAT). The five-year cumulative net drug budget impact for car+dar+dex was estimated to be €33.87 million (€30.66 million excluding VAT).

5. Patient Organisation Submission

A patient Organisation Submission was received from Multiple Myeloma Ireland.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that carfilzomib (Kyprolis®) in combination with daratumumab and dexamethasone not be considered for reimbursement, for this indication*.

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