Cost-effectiveness of avelumab (Bavencio®) for the treatment of metastatic Merkel cell carcinoma

The NCPE has issued a recommendation regarding the cost-effectiveness of avelumab (Bavencio®). Following assessment of the applicant's submission, the NCPE recommends that avelumab (Bavencio®) for the treatment of metastatic Merkel Cell Carcinoma not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation is conditional on the submission of supportive overall survival data from Part B of the Javelin Merkel 200 study for approval of avelumab for use in the first line setting. 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 (Merck KGaA) economic dossier on the cost effectiveness of avelumab (Bavencio®). 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.

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Summary

In September 2017, the EU commission granted conditional marketing authorisation for avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC). In March 2018, Merck KGaA submitted a dossier examining the cost-effectiveness of avelumab for the treatment of mMCC.

The authorised dose for this indication is 10mg/kg by intravenous infusion over 60 minutes every two weeks. Treatment should continue until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration could continue treatment. Avelumab is a humanised monoclonal antibody that specifically targets cancer cells through the inhibition of the immune checkpoint protein, PD-L1. Avelumab has an orphan designation

In the dossier, chemotherapy, in the form of carboplatin plus etoposide or single-agent carboplatin in first-line (1L) patients and topotecan in second-line (2L+) patients, was the comparator investigated. This was considered broadly appropriate by the NCPE.

1. **Comparative effectiveness of avelumab**

Currently there are no comparative trials of avelumab in patients with mMCC. The evidence to support efficacy was based on the JAVELIN Merkel 200 study. This study is an ongoing Phase II, open-label, multi-centre, single arm study aiming to evaluate the efficacy and safety of avelumab in adult patients with mMCC. JAVELIN is being conducted in two parts; Part A including patients who have failed at least one line of prior chemotherapy (2L+ cohort; n=88) with follow-up ongoing, and Part B in patients with no prior systemic therapy for metastatic disease (1L cohort; target enrolment: n=112). The primary endpoint for Part A (2L+ cohort) was confirmed best overall response (BOR) and for Part B (1L cohort) was durable response rate (DRR). Overall survival (OS) and progression-free survival (PFS) were included as secondary endpoints in both cohorts. Health related quality of life data was also collected using the EQ-5D-5L and the melanoma specific (in the absence of a MCC specific) FACT-M questionnaires.

For the 2L+ cohort (Part A) results are based on the most recent completed data-cut at (minimum for all patients) 18-months follow-up. For the 1L cohort (Part B) results are based on the latest data available. This included 39 patients, 29 of which had at least 3-months follow-up. The NCPE review team has concerns that the small number of patients and limited follow-up in the 1L cohort will lead to uncertainty in the clinical-effectiveness results for these patients. The median PFS was 2.7 months (95%CI 1.4,6.9) for the 88 patients with 18-month follow-up in the 2L+ cohort and 9.1 months (95%CI 1.9, NE) for the 39 patients with 3-month follow-up in the 1L cohort. Median OS was 12.6 months (95%CI 7.5,19.0) for the 2L+ cohort and not reached in the 1L cohort.

To establish estimates of relative effectiveness for use in the economic model, the applicant conducted a retrospective observational study (100070-Obs001) with the aim of investigating clinical outcomes of chemotherapy treatment. A naïve comparison with avelumab was performed based on analyses conducted by the applicant concluding that patient characteristics (other than previously received chemotherapy) do not appear predictive of outcomes in mMCC. The NCPE review team has concerns regarding the methods used to derive this conclusion and feel that a simulated treatment comparison may have been more appropriate. The NCPE review team recommends that any conclusions around comparative effectiveness made from a naïve comparison of single-arm studies should be treated with caution.

2. **Safety of avelumab**

Safety and tolerability was a secondary endpoint of the JAVELIN study. The most common treatment-emergent adverse events (TEAEs), of any grade, were fatigue, peripheral oedema, diarrhoea, nausea and decreased appetite. The most common grade ≥3 TEAEs were anaemia, hypertension and abdominal pain. Infusion-related reactions were reported in 19 patients (21.6%) in the 2L+ cohort and 10 patients (25.6%) in the 1L cohort and were mild or moderate in severity. The NCPE review team has concerns regarding the lack of long-term safety data.

3. Cost effectiveness of avelumab

Methods

For the cost-effectiveness analysis, separate models were conducted for the 2L+ and 1L cohorts. The key effectiveness inputs in the model were OS, PFS and time-on-treatment (ToT). Clinical efficacy inputs for avelumab were derived from JAVELIN for the 2L+ cohort, with the HRs described above applied to 2L+ data to derive estimates for the 1L cohort. Clinical efficacy inputs for chemotherapy were derived from the 100070-Obs001 study. Cost-effectiveness was investigated using a health state cost-utility model with a 40-year time horizon and cycle length of one week. The model simulates patients through three health states: 'Progression-free', 'Progressive disease' and 'Death'. The progression-free and progressed disease health states included three further sub-states; >100 days, 30-100 days and <30days until death. All patients enter the model in the "Progression-free" health state. From here, patients may transition to the other health states, or remain in this health state at each model cycle. Following progression, patients are unable to transition back to the "Progression-free" health state, and "Death" is an absorbing health state. Patient characteristics were derived from the JAVELIN study. Utility values were derived from the 2L+ cohort of the JAVELIN study and base case utilities were applied based on time to death. The same utilities were used for both the 2L+ and 1L cohorts and for avelumab and chemotherapy patients.

Survival outcomes from JAVELIN were extrapolated to the full time horizon of the model using spline models for the 2L+ cohort. These were considered to provide a flexible approach to modelling survival without imposing the assumption of a monotonic hazard function which may not be relevant in this case due to decreasing probability of progression and death indicated by the plateau in the survival curves. Parametric models were considered in sensitivity analyses. Data for the 1L cohort in the JAVELIN study was considered too immature to use in modelling, therefore clinical expert opinion was sought, by the applicant, to estimate hazard ratios (HRs) suitable for application to the 2L+ data to estimate OS and PFS. A HR of 0.8 was estimated for OS and as the clinicians did not feel able to provide an estimate for PFS a value of 1.0 was applied. The NCPE review team has concerns regarding the use of a HR based on clinician opinion only. Alternative modelling

approaches were investigated using empirical data from the 1L cohort in the JAVELIN study. Parametric survival models were fitted to the data from the 100070-Obs001 study to extrapolate OS and PFS outcomes for chemotherapy patients for both the 1L and 2L+ cohorts. The NCPE review team has concerns that, in both patient cohorts, the naïve comparison of the JAVELIN and 100070-Obs001 studies is unreliable due to imbalances in patient characteristics between the two studies, small numbers of patients and uncertainty caused by unmeasured variables that may be prognostic indicators. Parametric curves were fitted to the JAVELIN data to extrapolate ToT over the longer term. Based on clinical expert opinion the applicant base case assumes a third of patients remain on treatment at 2-years and that no patients remain on treatment beyond 5-years. Treatment duration was assumed to be the same in both patient cohorts. Alternative approaches were explored in scenario analyses.

Medical resource use frequencies were obtained via literature review using SCLC as a suitable proxy due to the lack of data for mMCC. Resource use was assumed to be the same irrespective of line of therapy. Costs were identified from Irish sources where possible and included drug acquisition, drug administration and monitoring costs, health state costs and costs of AEs.

Results

For the 2L+ cohort, the applicant base case estimates an incremental cost of €77,213 for a gain of 1.84 QALYs, resulting in an ICER of €41,894 per QALY. For the 1L cohort, the applicant base case estimates an incremental cost of €82,319 for a gain of 1.40 QALYs, resulting in an ICER of €58,679 per QALY.

Due to considerable uncertainty in the clinical evidence used to inform the economic model the NCPE suggested a number of changes to the model based on plausible alternative assumptions. This resulted in an increase in the ICER for the 2L+ cohort to €54,540 per QALY and €130,984 per QALY for the 1L cohort.

Sensitivity analysis

The applicant presented a probabilistic sensitivity analysis for each patient cohort. The probability of cost-effectiveness at willingness-to-pay thresholds of €45,000 and €20,000 per QALY was 65.5% and 0.20% respectively for the 2L+ cohort and 25.90% and 0.20% respectively for the 1L cohort. The applicant presented a variety of scenario analyses and performed appropriate sensitivity analyses. These analyses indicated that the model was particularly sensitive to the choice of OS curve for avelumab and assumptions regarding ToT. In addition, the model for the 1L cohort was also sensitive to assumptions regarding the HR applied for OS and ToT. The NCPE review team requested further sensitivity analyses using various alternative HRs for the 1L cohort. An analysis using a HR of 1 for OS (assuming no difference between the 2L+ and 1L cohorts) increased the ICER to €114,046 per QALY. An alternative approach capping the OS and PFS hazards for the 1L cohort by the hazards of the 2L+ cohort resulted in an ICER of €66,846 per QALY.

4. Budget impact of avelumab (specifically include list price of drug and the price per patient per year (or per treatment course as applicable)

The list price of avelumab (200mg vial) is €936.00. The average cost per treatment (including 23% VAT) is €4,888.50, with an average total cost of treatment per patient of €101,164.

The applicant estimates that there would be 6 eligible patients with mMCC in year 1, rising to 14 in year 5. The applicant estimates the 5-year gross budget impact to be approximately €2.1million. Due to the relatively low cost of chemotherapy there is negligible difference between the gross and net budget impact analyses.

5. Patient submission

No patient submissions were received during the course of this appraisal.

6. Conclusion

Following NCPE assessment of the company submission, avelumab (Bavencio®) is not considered cost-effective for the treatment of metastatic Merkel Cell Carcinoma and should not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation is conditional on the submission of supportive

overall survival data from Part B of the Javelin Merkel 200 study for approval of avelumab for use in the first line setting.