Cost-effectiveness of avelumab (Bavencio®) for first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of avelumab (Bavencio®) for first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.

Following assessment of the Applicant's submission, the NCPE recommends that avelumab (Bavencio®) 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 a review of the Applicant's (Merck Serono (Ireland) Ltd/Pfizer Healthcare Ireland) Health Technology Assessment 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 multidisciplinary team of clinicians, pharmacists, pharmacologists, information specialists 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 2021**

Summary

In June 2021, Merck Serono (Ireland) Ltd/Pfizer Healthcare Ireland submitted a dossier of clinical, safety and economic evidence on avelumab (Bavencio®) for first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy. Merck Serono Ltd/Pfizer Healthcare are seeking reimbursement on the Oncology Drugs Management Scheme. Final data was submitted by the Applicant in November 2021.

UC is the most common type of bladder cancer, also known as transitional cell bladder cancer and accounts for more than 90% of cases of bladder cancer. Avelumab is a monoclonal antibody inhibitor directed against PD-L1. PD-L1 attaches to T cells of the immune system, preventing them from attacking cancer cells. By targeting PD-L1, avelumab prevents the cancer cells from switching off the T cells, thereby increasing the ability of the T cells to kill the cancer cells. The recommended dose of avelumab is 800mg (four x 200mg vials) administered by intravenous (IV) infusion once every 14 days. Treatment should continue until disease progression or unacceptable toxicity.

The Applicant's anticipated place in therapy for avelumab is as a first-line maintenance treatment in patients with locally advanced or metastatic UC, who are progression-free following platinum-based chemotherapy. This is in line with the licenced indication for avelumab. The Review Group is in agreement with the Applicant's proposed place in therapy for avelumab. There are no other licenced first-line maintenance treatments for this population in Ireland. The standard of care, in Ireland, following platinum-based chemotherapy, for patients who achieve a complete response, partial response or stable disease is to observe patients until they progress (this corresponds with best supportive care (BSC)). Thereafter, patients will receive subsequent line(s) of treatment (if eligible and fit enough to tolerate further treatment). Subsequent treatment options available in Ireland include the PD-1 inhibitors pembrolizumab and atezolizumab.

Clinical opinion, sought by the Applicant, demonstrated that platinum-based chemotherapy is the first-line of treatment for patients with UC, unless there is a contraindication. Clinicians said the availability of avelumab may alter clinician's typical approach in treating

metastatic UC in that they may reduce the number of cycles of chemotherapy and switch to maintenance avelumab instead.

1. Comparative effectiveness of avelumab

Clinical evidence is available from one phase III, multicentre, multinational, randomised, open-label, parallel-arm trial of avelumab plus BSC compared with BSC (reflective of BSC Ireland). The JAVELIN Bladder 100 trial randomised 700 patients (n=350 in the avelumab plus BSC arm; n=350 in the BSC arm) and was designed with two co-primary populations: 1) all randomised patients (overall population) and 2) patients with PD-L1-positive tumours[1] (a subgroup of the overall population). The primary endpoint was overall survival (OS) in patients with locally advanced or metastatic UC in both populations. At the time of the interim analysis, median duration of follow-up for OS was approximately 20 months. A statistically significant prolonged OS in the avelumab plus BSC arm (median OS 21.4 months, 95% confidence interval [CI] 18.9 to 26.1) compared with the BSC arm (median OS 14.3 months, 95% CI 12.9 to 17.9), in the overall population was demonstrated. Similar findings for OS were reported in the population of patients with PD-L1 positive tumours. Progression-free survival (PFS), a secondary outcome of the JAVELIN Bladder 100 trial, was also statistically significantly longer with avelumab plus BSC, in both populations. The observed objective response rate was statistically significantly greater in the avelumab plus BSC arm compared with the BSC arm. The median duration of response for patients who responded was not reached in either treatment arm, in both patient populations.

The Review Group note that no clear benefit of avelumab treatment in the population of patients with PD-L1 negative tumours was seen in exploratory analyses (unstratified hazard ratio for OS: 0.86; 95% CI: 0.62, 1.18).

Overall, patient reported health related quality of life was similar in patients treated with avelumab plus BSC and those receiving BSC. The results should however be interpreted with

[1] Positivity for PD-L1 was defined as meeting one of the following criteria: expression in at least 25% of tumour cells, expression in at least 25% of tumour-associated immune cells if the percentage of immune cells was more than 1%, or expression in 100% of tumour-associated immune cells if the percentage of immune cells was no more than 1% (using the Ventana SP263 assay).

caution due to the open label study design and thus the inherent risk of bias in patient reported outcomes.

The Review Group highlight a number of important limitations to the JAVELIN Bladder 100 trial, and its generalisability to clinical practice in Ireland.

- There is an imbalance in the use of second-line treatments in the two arms. More patients in the BSC arm received subsequent anti-cancer drugs (61.7% in the BSC arm vs 42.3% in the avelumab plus BSC arm, and of these 43.7% were PD-1 or PD-L1 treatments in the BSC arm vs. 6.5% in the avelumab plus BSC arm). The impact of these various treatments on outcomes is unclear.
- The majority of patients in the BSC arm did not receive second-line treatment with immunotherapy (the current standard of care in Ireland).
- The trial data (for OS in particular) is immature with data from interim analyses presented and a median follow-up of 19.6 months in the avelumab plus BSC arm and 19.2 months in the BSC arm. This leads to uncertainty in the survival extrapolations and model outcomes.

No additional clinical trials of relevance were identified through the systematic review, and no evidence synthesis was performed.

2. Safety of avelumab

The general class safety profile for PD-L1 inhibitors is considered well known. In JAVELIN Bladder 100 trial, the incidence of all grades of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) was higher in the avelumab plus BSC arm compared to the BSC arm, in both patient populations. The most commonly reported TEAEs in the avelumab plus BSC arm were fatigue (17.7%), pruritus (17.2%) and urinary tract infections (17.2%), and in the BSC arm, they were urinary tract infections (10.4%), back pain (9.9%) and constipation (9.0%). No new safety concerns were identified and the adverse event profile is similar to those observed for immune checkpoint inhibitors previously approved for first and second-line treatment of locally advanced or metastatic UC.

3. Cost effectiveness of avelumab

Cost effectiveness of avelumab was assessed using a de novo cohort level partitioned survival model with a 25-year time horizon. The cycle length was one week; a half-cycle correction was not applied. The comparator was BSC. Population characteristics were based on the JAVELIN Bladder 100 trial. There are three mutually exclusive health states: pre-progression, post-progression, and death. Patients enter in the pre-progression state, and remain here until disease progression or death. Patients cannot transition to an improved health state. Movement through the health states is based on the extrapolated PFS and OS survival curves from JAVELIN Bladder 100.

Treatment duration was modelled using parametric extrapolation of time to treatment discontinuation (TTD) data from JAVELIN Bladder 100. No maximum treatment duration for avelumab was specified in the JAVELIN Bladder 100 trial, however, the Applicant assumed a maximum treatment duration of 10 years. Upon disease progression, a proportion of patients in both arms are assumed to receive various second and subsequent lines of treatment. The proportion of patients receiving subsequent treatments, and the breakdown of treatments received, are important determinants of the total costs.

A key limitation of the model is the immaturity of the OS data from the JAVELIN Bladder 100 trial, and the resultant uncertainty in the survival extrapolations. There are a limited number of health states in the model, and the clinical pathway for patients, particularly to second-line treatment and terminal care, is simplistic as a result. The full impact of subsequent lines of treatment cannot be explicitly incorporated into the model, and therefore the model cannot clearly define the survival benefit directly attributable to the intervention as distinct from subsequent treatments.

Health outcomes were measured as incremental quality-adjusted life year (QALY) gains. Health related quality of life data was collected during the JAVELIN Bladder 100 trial using the EQ-5D-5L questionnaire. These responses were ‘cross-walked’ to the EQ-5D-3L, and valued using UK value set. Utility was applied based on progression status and adjusted for increasing age. Disutility values for TRAEs were sourced from the literature.

The Review Group made a number of changes to the Applicant's base case model, including alternative choices for extrapolation models for OS and TTD; amending the application of discounting; and updating the application of subsequent treatment costs to match the JAVELIN Bladder 100 trial data.

Results of the Applicant's base case, and the Review Group adjusted base case, are illustrated in Tables 1 and 2, respectively. The probability of cost-effectiveness is presented in Table 3. In the probabilistic analysis, 7.85% of simulations predict that avelumab is associated with fewer QALYs, and higher costs, than BSC.

Table 1: Results of the Applicant's deterministic base case cost-effectiveness analysis of avelumab plus BSC versus BSC

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
BSC	53,402	1.75			
Avelumab	122,195	2.34	68,793	0.59	**116,360**

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care
Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at the list price of all drug components.

Table 2: Results of the Review Group deterministic adjusted base case cost-effectiveness analysis of avelumab plus BSC versus BSC

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
BSC	51,309	1.51			
Avelumab	140,663	2.09	89,354	0.59	**152,709**

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care
Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at the list price of all drug component

Table 3: Probability of cost-effectiveness

	Probability of cost-effectiveness at a threshold of €20,000 / QALY	€45,000 / QALY
Review Group adjusted base case	0%	0%
Applicant base case	0%	3.55%

QALY: quality adjusted life year

4. Budget impact of avelumab

The price to wholesaler per 200mg vial of avelumab is €896.63. The cost per cycle (using a flat dose of 800mg, (i.e. four x 200mg vials) is €4,214.16 (including VAT). The cost per patient per year of treatment is €106,246 (based on the modelled mean TTD, adjusted to account for treatment intensity in the JAVELIN Bladder 100 trial).

The Applicant estimated that approximately 95 patients would be treated with avelumab each year (five-year cumulative total n=475).

The Applicant estimated the gross budget impact for avelumab to be €5,046,708 in year one increasing to €4,303,817 in year five, and a cumulative five-year gross budget impact estimated to be €32,565,383 including VAT. Since avelumab is an add-on treatment to BSC, the net budget impact is equal to the gross budget impact. The Applicant also presented a scenario which includes cost offsets of second-line immunotherapy due to use of avelumab maintenance (based on the assumption that patients can receive one course of immunotherapy (as second-line treatment) funded through the HSE). In this scenario, the five-year net budget impact including VAT is €17,929,340. This analysis does not account for confidential discounts in place for these immunotherapies, and thus is an underestimate of the actual net budget impact.

5. Patient submission

No patient organisation submission was received during the course of this assessment.

6. Conclusion

The NCPE recommends that avelumab (Bavencio®), for first-line maintenance treatment of adult patients with bladder cancer who are disease free following platinum-based chemotherapy, 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.