Cost-effectiveness of avelumab (Bavencio®) in combination with axitinib (Inlyta®) for the first-line treatment of adult patients with advanced renal cell carcinoma

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of avelumab (Bavencio®) in combination with axitinib (Inlyta®). Following assessment of the Applicant's submission, the NCPE recommends that avelumab (Bavencio®) in combination with axitinib (Inlyta®) 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 HSE asked the NCPE to carry out an assessment of the Applicant's (Merck Serono Ltd/Pfizer Healthcare Ireland) Health Technology Assessment dossier on avelumab (Bavencio®) in combination with axitinib (Inlyta®). 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.

National Centre for Pharmacoeconomics **June 2021**

Summary

In July 2020, Merck Serono Ltd/Pfizer Healthcare Ireland submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of avelumab in combination with axitinib (avelumab+axitinib) for the first-line treatment of adult patients with advanced renal cell carcinoma (aRCC). Reimbursement of avelumab is sought on the Oncology Drug Management System.

Avelumab is a human immunoglobulin G1 monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic $CD8^+$ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also been shown to induce natural killer cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity. Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth and metastatic progression of cancer.

Avelumab is administered by intravenous (IV) infusion at a dose of 800mg once every two weeks. Concurrent treatment with axitinib is at a dose of 5mg twice daily orally. Treatment should continue until disease progression or unacceptable toxicity.

In the full licensed population (i.e. patients in all risk groups), the comparators are sunitinib monotherapy, pazopanib monotherapy and pembrolizumab in combination with axitinib (pembrolizumab+axitinib). Of note, the NCPE recently assessed the cost-effectiveness of pembrolizumab+axitinib in the first-line setting; this combination is currently under review for reimbursement by the HSE. The Applicant provided comparisons for two comparators which are licensed specifically for use in the intermediate-/poor-risk subgroup (as defined by the International Metastatic RCC Database Consortium (IMDC) score). The Review Group considered one of these comparators, nivolumab in combination with ipilimumab (nivolumab+ipilimumab), to be the relevant comparator in this population. The Review Group do not consider the other comparator, cabozantinib, to be a relevant comparator; it is not reimbursed in Ireland in this setting.

1. Comparative effectiveness of avelumab in combination with axitinib

The clinical efficacy of avelumab+axitinib compared with sunitinib was examined in JAVELIN Renal 101 which is an ongoing phase III, randomized, multicentre, open label study in the first-line treatment of aRCC in adults (irrespective of PD-L1 expression status) across all IMDC risk groups. Patients (all risk groups) were randomised to receive avelumab IV 800mg once every two weeks in combination with axitinib 5mg twice daily orally (n=442) or sunitinib 50mg once daily orally on days 1 to 28 of a 42-day cycle (n=444). Treatment was continued until disease progression or unacceptable toxicity. However, treatment could continue beyond confirmed disease progression if a patient was experiencing clinical benefit.

Patient characteristics were generally balanced between arms. IMDC risk category was favourable for 21.4% of patients, intermediate for 61.7%, and poor for 16.1%. The primary efficacy endpoints were progression-free survival (PFS) and overall survival (OS) in patients with PD-L1+ tumours, as assessed by blinded independent central review. Key secondary endpoints included PFS and OS in patients irrespective of PD-L1 expression.

The Applicant presented efficacy data from the second interim analysis (IA2), with a data cut-off date of 28 January 2019, for patients (all risk groups) irrespective of PD-L1 expression status. This is in line with the population for which the treatment is licensed. At IA2 the minimum duration of follow-up was 13 months, 242 patients (54.8%) had discontinued both avelumab and axitinib and 336 patients (75.7%) had discontinued sunitinib. The primary reason for discontinuation was disease progression. Avelumab+axitinib demonstrated a benefit over sunitinib in PFS (hazard ratio (HR) of 0.69; 95% CI 0.57 to 0.83; p<0.0001) and this result was consistent across all subgroups including prognostic risk groups. At a median OS follow-up of 19 months, OS data were immature (HR of 0.80; 95% CI 0.62 to 1.03). The long-term OS benefit of avelumab+axitinib is unknown.

Estimates of relative efficacy vs sunitinib for the cost-effectiveness evaluation were based on the JAVELIN Renal 101 trial. The efficacy of pazopanib and pembrolizumab+axitinib in the full licensed population (all risk groups) and nivolumab+ipilimumab in the intermediate-/poor-risk population were based on results of a network-meta analysis (NMA). Within the

full licensed population (all risk groups), results of the NMA indicated that avelumab+axitinib improves OS and PFS compared with pazopanib, though the difference for OS was not statistically significant. Compared with pembrolizumab+axitinib, avelumab+axitinib is associated with worse OS (not statistically significant) and no significant difference in the duration of PFS. The results of the NMA in the intermediate-/poor-risk population indicate that avelumab+axitinib is associated with worse OS than nivolumab+ipilimumab (not statistically significant) and no significant difference in the duration of PFS. NMA outputs are uncertain mainly due to differences in subsequent treatment use across trials.

2. Safety of avelumab in combination with axitinib

Safety of avelumab+axitinib has been evaluated in 489 patients with aRCC in two clinical studies; JAVELIN Renal 100 (a phase 1b dose finding study) and JAVELIN Renal 101 (IA1, data cut-off date 20 June 2018). The most common adverse reactions were diarrhoea (62.8%), hypertension (49.3%), fatigue (42.9%), nausea (33.5%), palmar-plantar erythrodysaesthesia (33.3%), dysphonia (32.7%), decreased appetite (26.0%), hypothyroidism (25.2%), cough (23.7%), stomatitis (22.5%), headache (21.3%), dyspnoea (20.9%), and arthralgia (20.9%). Three cases of myocarditis (two of which were fatal) and two cases of fatal immune-related pancreatitis were reported. The safety profile of the combination was mostly consistent with the known safety profiles of avelumab and axitinib monotherapies with some exceptions, which included higher reported frequencies for diarrhoea, hypothyroidism and increased alanine aminotransferase.

Infusion related reactions have been reported for avelumab in clinical trials. Therefore, the Summary of Product Characteristics advises that patients receive antihistamine and paracetamol prior to at least the first four infusions of avelumab.

3. Cost effectiveness of avelumab in combination with axitinib

A partitioned survival model with a 40-year time horizon was used. The patient starting age was 60.8 years. OS, PFS and time-on-treatment (ToT) were based on Kaplan-Meier data from JAVELIN Renal 101. Patient characteristics were derived from JAVELIN Renal 101 and are in line with the population for which the treatment is licensed (i.e. patients (all-risk

groups) irrespective of PD-L1 expression status). Utilities were estimated from JAVELIN Renal 101. The Review Group identified a number of limitations in the Applicant's cost-effectiveness model, which were addressed in the NCPE adjusted base case. The Review Group concurred with the Applicant's choice of log-normal extrapolation for the sunitinib PFS data. Based on clinical opinion to the Review Group, the log-normal model was chosen to extrapolate the avelumab+axitinib PFS data. The exponential model was chosen to extrapolate the OS data for both avelumab+axitinib and sunitinib.

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively.

Table 1 NCPE adjusted base case analysis - Avelumab+axitinib vs comparators (Pairwise analysis)

	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licenced population (All-risk group)					
Avelumab+axitinib	323,681	3.36			
Sunitinib	159,964	2.80	163,717	0.56	291,579
Pazopanib	151,328	2.99	172,352	0.36	472,842
Pembrolizumab+axitinib	422,268	4.55	-98,587	-1.20	Less costly, less effective[1]
Intermediate-/poor-risk group					
Avelumab+axitinib	291,089	2.89			
Nivolumab+ipilimumab	226,127	3.88	64,962	-0.99	Dominated[2]

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year
Figures in the table are rounded, and so calculations may not be directly replicable
[1] Avelumab+axitinib is less costly and less effective than pembrolizumab+axitinib
[2] Avelumab+axitinib is more costly and less effective than nivolumab+ipilimumab

Table 2 Applicant base case analysis - Avelumab+axitinib vs comparators (Pairwise analysis)

	Total Costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licenced population (All-risk group)					
Avelumab+axitinib	323,434	3.64			
Sunitinib	163,537	3.10	159,897	0.54	296,482
Pazopanib	155,173	3.35	168,261	0.29	579,453
Pembrolizumab+axitinib	444,412	5.20	-120,978	-1.56	Less costly, less effective[1]
Intermediate-/poor-risk group					
Avelumab+axitinib	292,152	3.27			
Nivolumab+ipilimumab	233,057	4.69	59,094	-1.42	Dominated[2]

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year
Figures in the table are rounded, and so calculations may not be directly replicable
[1] Avelumab+axitinib is less costly and less effective than pembrolizumab+axitinib
[2] Avelumab+axitinib is more costly and less effective than nivolumab+ipilimumab

In both the NCPE-adjusted and Applicant's base case, the probabilistic ICERs of avelumab+axitinib vs comparators were similar to the deterministic ICERs. The probability of cost effectiveness, at a willingness-to-pay threshold of €45,000 per QALY, vs sunitinib is 0.7% and vs pazopanib is 0.4%.

4. Budget impact of avelumab in combination with axitinib

The price to wholesaler for avelumab 20mg/ml concentrate for solution for infusion (10ml vial) is €896.63 per vial.

In the budget impact model, the mean ToT each year for avelumab+axitinib and comparators were estimated using the ToT curves from the cost-effectiveness model. Relative dose intensities for avelumab+axitinib and sunitinib were derived from JAVELIN Renal 101. The total drug acquisition cost to the HSE, of avelumab+axitinib (including 5.5% rebate, VAT, pharmacy fees and wholesale fees), is approximately €300,000 per patient per treatment course (circa 23.5 months).

The Applicant predicted that a total of 889 patients would be eligible for treatment over five years. On review of the available incidence rate data and as informed by clinical opinion, the Review Group instead predicted that a total of 989 patients would be eligible for treatment over five years.

The Applicant provided market share predictions for avelumab+axitinib and its comparators, under the assumption that pembrolizumab+axitinib is reimbursed. The Applicant estimated the 5-year cumulative gross budget impact to be €19.86 million and the 5-year cumulative net budget impact to be €8.02 million. Pembrolizumab+axitinib is not currently reimbursed in Ireland for this indication. The market share predictions for avelumab+axitinib are thus higher in the NCPE adjusted base case. The Review Group made changes to comparator ToT and relative dose intensity data (so that these would be in line with those in the cost effectiveness model). Under the Review Group assumptions, the estimated 5-year cumulative gross budget impact is €50 million and the 5-year cumulative net budget impact is €36.76 million. In a scenario where pembrolizumab+axitinib is assumed to be reimbursed

(and all other Review Group assumptions are maintained), estimated gross and net impacts are €22.09 million and €9.24 million, respectively.

5. Patient submissions

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

The NCPE recommends that avelumab in combination with axitinib 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 Medicinal Goods) Act 2013.