Cost-effectiveness of pembrolizumab (Keytruda®) for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

The NCPE has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®). Following assessment of the applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) be considered for reimbursement if 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (MSD) economic dossier on the cost effectiveness of pembrolizumab (Keytruda®). 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 **March 2019**

Summary

In October 2018, MSD Ltd. submitted a dossier of clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of pembrolizumab (Keytruda®) for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Final data was submitted by the Applicant in January 2019. MSD are seeking reimbursement for pembrolizumab (Keytruda®) in the hospital setting.

Pembrolizumab (Keytruda®)

Pembrolizumab is a humanised monoclonal antibody (mAb) which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2, expressed on the surface of the tumour cells. Disruption of this PD-1 pathway by pembrolizumab allows the immune system to mount a response against the tumour cells by potentiating T-cell immune responses, including anti-tumour responses.

The authorised dose of pembrolizumab for this indication is 200 mg by intravenous infusion (IV) every three weeks. Treatment should be continued for as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Pembrolizumab is formulated as a 100 mg powder for concentrate for solution for infusion.

Standard of care (SOC) chemotherapy, in the form of paclitaxel and docetaxel chemotherapy, was the comparator investigated. This was considered appropriate by the NCPE Review Group and in line with the SOC in the Irish setting.

1. Comparative effectiveness of pembrolizumab

Relative efficacy outcomes for the comparison with paclitaxel and docetaxel were based on the Phase III, open-label, randomised trial, Keynote-045.

In Keynote-045, patients with metastatic or locally advanced/unresectable urothelial carcinoma that had recurred or progressed following platinum-containing chemotherapy were randomised in a 1:1 ratio to receive either pembrolizumab 200 mg IV (n=270), or

investigator's choice of paclitaxel 175 mg/m^2 IV (n=84), docetaxel 75 mg/m^2 IV (n=84) or vinflunine 320 mg/m^2 IV (n=87), all administered every three weeks. In the trial, treatment with pembrolizumab beyond progressive disease was permitted in the event of continuing clinical benefit, and treatment duration was capped at a maximum of 35 cycles (2 years continuous treatment). The latest data-cut from Keynote-045 is based on the 26th October 2017 database lock. Results are presented for the ITT population; however, for the purpose of the economic analysis, data pertaining to the Irish standard of care cohort only (i.e. excluding vinflunine) was utilised.

The co-primary endpoints of Keynote-045 were progression free survival (PFS), defined as time from randomisation to the first documented disease progression per RECIST 1.1 based on blinded independent central review (BICR) or death due to any cause, and overall survival (OS), defined as the time from randomisation to death due to any cause. Pembrolizumab was associated with an increase in OS compared to the comparator arm. Median OS was 10.1 months (95% CI 8.0, 12.3) in the pembrolizumab arm and 7.3 months (95% CI 6.1, 8.1) in the control arm. Pembrolizumab did not demonstrate a statistically significant improvement in PFS compared to the control arm. Median PFS was 2.1 months (95% CI 2.0, 2.2) in the pembrolizumab arm and 3.3 months (95% CI 2.4, 3.6) in the control arm.

2. Safety of pembrolizumab

Safety and tolerability was evaluated as a secondary endpoint in Keynote-045 in patients who received at least one dose of pembrolizumab. Safety analysis is based on the 7th September 2016 data-cut.

Pembrolizumab was associated with a slightly lower incidence of AEs compared to the control arm; 93.2% versus 98.0%, respectively. The most frequent AEs observed in the pembrolizumab arm were fatigue (25.6%), pruritus (23.7%), decreased appetite (21.4%) and nausea (20.7%). In the control arm, the most commonly observed AEs were alopecia (38.8%), anaemia (35.7%), fatigue (33.7%), constipation (31.8%), nausea (28.6%), decreased appetite (20.8 %) and asthenia (20.8%). A lower proportion of patients in the pembrolizumab arm experienced Grade ≥3 AEs (52.3%) compared to the control arm

(62.7%). Fewer patients in the pembrolizumab arm experienced drug related AEs when compared to the control arm (60.9% vs 90.2%, respectively). A total of 22 (8.3%) patients in the pembrolizumab arm and 32 (12.5%) patients in the control group had an AE resulting in treatment discontinuation. The most common AEs leading to discontinuation were pneumonitis (1.9%) in patients treated with pembrolizumab, and peripheral sensory neuropathy (2.0%) and peripheral neuropathy (1.6%) in patients who received chemotherapy. A total of 13 patients (4.9%) in the pembrolizumab arm and 8 patients (3.1%) in the control group had AEs resulting in death within 90 days of the last dose.

Overall, pembrolizumab had a favourable safety profile compared to control in the Keynote-045 trial, with a lower incidence of treatment-related AEs and Grade 3-5 AEs. The safety profile of pembrolizumab was in line with previous studies of pembrolizumab and no new safety signals were raised.

3. Cost effectiveness of pembrolizumab

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from Keynote-045. Cost-effectiveness was based on a cost-utility partitioned survival model with a 35-year time horizon and a cycle length of one week. The model simulates patients through three mutually exclusive health states; pre-progression, post-progression and death. Death is an absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from Keynote-045. Treatment duration is based on time on treatment (ToT) data from the Keynote-045 trial.

The time horizon of this trial was shorter than the time horizon of the model, and so considerable extrapolation of the data was required. OS data was adjusted for crossover. Analysis of diagnostic plots (cumulative, log-cumulative hazard, and Schoenfeld residual plots), indicated that a proportional hazards assumption would not be suitable for modelling survival. Thus, a 2-phase piecewise modelling approach was adopted in order to capture the changing non-constant hazard over time. In the Applicant's base-case, the first 40 weeks of

OS data were modelled using a fitted Kaplan-Meier curve, with a log-normal curve fitted to the remaining data. For PFS, Kaplan-Meier data was used directly until week 27, with a Weibull curve fitted to the remaining data.

A systematic literature review was conducted to identify relevant cost and resource use data for use in the economic model. The data employed in the model is based on a number of sources including: Keynote-045, national databases, and published sources. Costs included in the model comprise of drug acquisition, administration, and monitoring costs, hospital and home care resource use, and management of AEs. Additional costs are included for subsequent treatment and a once-off terminal care cost is applied on entering the death state. The AEs considered in the model included Grade 3-5 AEs which occurred in at least 5% of patients in either treatment arm. In addition, Grade ≥ 2 diarrhoea and febrile neutropenia were also included. In the base-case, utility was modelled using a time-to-death approach. Future costs and health-related outcomes were discounted at a rate of 5% per annum, in line with national guidelines.

Analyses presented in this summary document are based on the list prices of the interventions. In the Applicant base-case, the ICER for pembrolizumab versus SOC was €86,311/QALY (incremental costs €63,659, incremental QALYs 0.74). The NCPE implemented a number of changes to the model, resulting in a final ICER of €105,010/QALY (incremental costs €68,129, incremental QALYs 0.65).

The Applicant presented a probabilistic sensitivity analysis. The probability of cost-effectiveness at a willingness to pay threshold of €20,000 and €45,000 was 0%. The Applicant also presented a variety of scenario analyses and preformed appropriate sensitivity analyses. Results of this analysis indicate that the inputs with greatest impact on the ICER are those related to the extrapolation of OS, pembrolizumab dose intensity and parameters relating to time on treatment estimation. The discount rate on health outcomes was also a significant driver, highlighting the proportion of gains which are accrued in the extrapolation phase. The NCPE performed a number of additional sensitivity analyses to test assumptions made in the model.

4. Budget impact of pembrolizumab

The price to wholesaler (PTW) of a 100 mg vial of pembrolizumab is €3,286.81. This price is further subject to VAT. The total cost to the HSE, based on a mean of 10.5 treatment cycles and inclusive of all relevant rebates and VAT, is €81,102.

The Applicant estimates that between 22 and 26 patients will be treated each year, with a decreasing annual incidence. The projected gross budget impact, based on these estimates and inclusive of only drug acquisition costs, is €1,544,321 (Year 1), €1,855,291 (Year 2), €1,804,222 (Year 3), €1,754,559 (Year 4), and €1,706,263 (Year 5). This results in a cumulative budget impact of €8,664,657 over five years. An estimated net budget impact was also presented by the Applicant. This is based on the assumption that pembrolizumab will replace current standard of care. The cumulative five year net budget impact, accounting for only drug acquisition costs, is €8,464,946. Given the relatively low costs of the off-patent comparator treatments, the net budget impact of pembrolizumab is considerable.

The Review Group consider the gross budget impact presented by the Applicant to be potentially underestimated. This is largely due to the fact that it does not account for patients who progress to Stage IV from earlier stages. In light of this, a scenario was presented by the Applicant, whereby the estimated patient population increases to between 42 and 47 patients per year. Incorporating these population estimates results in a five year cumulative gross budget impact of €16,132,204. The Review Group highlight the sensitivity of the budget impact to assumptions surrounding population estimates; treating approximately 20 additional patients per annum increases the 5-year cumulative gross budget impact by over €7 million.

5. Patient submissions

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

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommend that pembrolizumab (Keytruda®) be considered for reimbursement if 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.