Cost-effectiveness of pembrolizumab (Keytruda ®) for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection

The National Centre for Pharmacoeconomics (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*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Merck Sharpe and Dohme (MSD) Ltd) 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.

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

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Summary

In September 2019, MSD Ltd submitted a dossier of clinical, safety and economic evidence on pembrolizumab (Keytruda ®) for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection. For this indication, pembrolizumab is administered intravenously, either as 200mg dose every three weeks or 400mg dose every six weeks, until disease recurrence, unacceptable toxicity, or for a duration of up to one year. There are no drugs reimbursed, in Ireland, for the adjuvant treatment of melanoma. In the submission, pembrolizumab was compared to routine surveillance (standard of care in Ireland) in the treatment of eligible patients with high risk stage III melanoma (following complete resection). A scenario analysis compared pembrolizumab to dabrafenib in combination with trametinib in a population with BRAF mutation positive disease. Nivolumab is also considered a relevant comparator for the entire eligible population. This was not included in this submission. It was not feasible to indirectly compare nivolumab with pembrolizumab.

1. Comparative effectiveness of pembrolizumab (Keytruda ®)

Relative efficacy for the comparison of pembrolizumab with routine surveillance was derived from an interim analysis from the KEYNOTE-054 trial. This was a single randomised, double blinded, placebo-controlled, phase III study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). The trial was designed to assess whether post-surgery adjuvant therapy with pembrolizumab (200mg every 3 weeks) improves recurrence free survival (RFS) as compared with placebo for patients with high risk stage III melanoma. Placebo is considered a proxy for routine surveillance. The CHMP accepted RFS efficacy outputs based on a previously unplanned interim analysis at a median of 16 months of follow-up. In the intention to treat (ITT) population the median RFS had not been reached in the pembrolizumab arm compared with 20.4 months (95% CI, 16.2, not reached) in the placebo arm. The interim results demonstrate that RFS was increased with pembrolizumab compared with placebo (HR 0.57, 98.4% CI, 0.43 to 0.74; p<0.0001). At 12 months the RFS rate in the pembrolizumab arm was 75.4% (95% CI, 71.3 to 78.9) and 61.0% (95% CI, 56.5 to 65.1) in the placebo arm. At 18 months the RFS rate was 71.4% (95% CI, 66.8,75.4) in the pembrolizumab arm and 53.2% (95% CI,47.9 to 58.2) in the placebo arm. The Review Group highlight that the RFS data are

immature; this limits understanding of the long-term treatment effects associated with pembrolizumab. Also, overall survival (OS) and distant metastases free survival data are immature. The Review Group highlight that several members of the CHMP did not agree with the CHMP's positive opinion of pembrolizumab citing that the duration of follow up in the KEYNOTE-054 trial was not sufficient, given that recurrences are often not observed before three years. Further the licensed indication reflects a broader population than was included in the clinical trial.

2. Safety of pembrolizumab (Keytruda ®)

In the KEYNOTE-054 trial, adverse events (AEs) of any grade that were considered to be related to the trial regimen occurred in 77.8% of patients in the pembrolizumab group and in 66.1% of patients in the placebo group. Drug related grade 3 to 5 AEs were reported in 14.5% of the patients in the pembrolizumab arm compared with 3.4% of patients in the placebo arm. Drug related serious adverse events were reported in 13% of patients in the pembrolizumab arm compared with 1.2% in the placebo arm. There was one treatment-related death due to myositis in the pembrolizumab group. A greater number of patients in the pembrolizumab arm (12.2%) experienced a treatment related AE which led to treatment discontinuation than in the placebo arm (1.6%). Immune-related AEs were reported in 34% of patients in the pembrolizumab arm and 7.6% in the placebo arm. The incidence of grade 3 or 4 immune-related adverse events was 7.1% in the pembrolizumab arm and most events resolved within 2 months after the last dose of pembrolizumab, findings which are similar to those previously observed in advanced melanoma. The safety profile of pembrolizumab in KEYNOTE-054 was found to be generally consistent with the established safety profile of pembrolizumab.

3. Cost effectiveness of pembrolizumab (Keytruda ®)

Methods

A four-state transition model was used to estimate the cost effectiveness of pembrolizumab compared to routine surveillance in a population of patients with resected stage III melanoma. In a scenario analysis, pembrolizumab was compared to dabrafenib in combination with trametinib in patients with BRAF mutation positive disease. The model structure allowed for a differentiation according to the type of recurrence; this is a

significant prognostic factor in stage III melanoma. Clinical data used in the model primarily included the KEYNOTE-054 study supplemented with registry data, KEYNOTE-006 and indirect evidence from a network meta-analysis (NMA). The model included drug related costs (costs for drug acquisition and administration) and costs associated with disease management (including costs of medical resource use and subsequent lines of therapy). Costs associated with the management of AEs as well as a once-off cost for terminal care were also incorporated.

Results

In the Applicant's base-case, pembrolizumab is dominant over routine surveillance in the overall patient population as it provides 2.02 more quality-adjusted life years (QALYs) and is less expensive (- €11,414). For BRAF mutation positive patients, pembrolizumab (vs. dabrafenib in combination with trametinib) is more costly (€64,156), provides more QALYs (0.75) and is associated with an ICER of €85,322 per QALY. The model indirectly predicts an OS benefit due to a longer time spent in the RF health state and thus fewer patients are projected to develop disseminated disease and die. The parameters that have most influence on the incremental QALY gain are the time horizon and the survival extrapolation methods. Those which have the most influence on incremental costs are the cost of subsequent therapies, the extrapolation methods, and the time horizon. The Review Group consider that the Applicant's extrapolation of the immature treatment effect data over the lifetime of the model (46 years) may over represent the lifetime benefit of adjuvant pembrolizumab. The Review Group attempted to minimise this through the application of a treatment waning effect to patients who remain in the RF health state beyond 3 years. However, there remains much uncertainty. This is evident when various time horizons were considered. Time horizons longer than 7 years result in pembrolizumab dominating routine surveillance in the Applicant's base case. The Review Group note that reducing the time horizon to 5 and 2 years results in the ICER for pembrolizumab versus routine surveillance increasing in the Applicant's base case (€20,190 per QALY and €773,675 per QALY).

4. Budget impact of pembrolizumab (Keytruda ®)

Pembrolizumab is administered intravenously, either as a 200mg dose every 3 weeks or a 400mg dose every 6 weeks as a hospital-only treatment in the outpatient setting. Should

pembrolizumab be reimbursed, Irish clinical opinion suggests that it will be administered intravenously every 6 weeks (400mg dose) in a day case setting for up to one year. The proposed price to wholesaler for pembrolizumab is €3,286.81 (ex. VAT) per 100mg vial. The total cost, exclusive of VAT, for a 200mg and 400mg dose is €7,724 and €15,448, respectively. The drug cost of pembrolizumab monotherapy per patient to the HSE is dependent on the time on treatment. Assuming pembrolizumab infusions are administered every 6 weeks (400mg) and based on the mean duration of treatment in the KEYNOTE-054 trial, the cost to the HSE per patient is €108,136 inclusive of VAT and rebate. Based on the Applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €40.23 million at an 80% market share up to €50.28 million at a 100% market share. Administration costs associated with pembrolizumab inflate the 5-year cumulative gross budget impact to €53.87 million at a 100% market share. It was not possible to accurately present cost offsets from the advanced melanoma setting as the impact of the use of pembrolizumab as adjuvant therapy on subsequent treatment in the metastatic setting is unknown.

5. Patient submissions.

No patient submissions were received for this assessment.

6. Conclusion

The NCPE recommends that pembrolizumab 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.