Cost-effectiveness of dostarlimab (Jemperli®) monotherapy for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of dostarlimab (Jemperli®). Following assessment of the Applicant's submission, the NCPE recommends that dostarlimab (Jemperli®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (GlaxoSmithKline) Health Technology Assessment of dostarlimab (Jemperli®). 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.*

National Centre for Pharmacoeconomics **March 2023**

Summary

In June 2022, GlaxoSmithKline (Ireland) Ltd submitted a dossier examining the clinical effectiveness, cost-effectiveness and budget impact of dostarlimab monotherapy for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. A conditional marketing authorisation was granted by the European Medicines Agency for dostarlimab for this indication in April 2021. Reimbursement is sought under the Oncology Drugs Management System.

Dostarlimab is a humanised, monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor. By inhibiting the binding of PD-1 to PD-L1 and PD-L2, dostarlimab blocks the PD-1 signalling pathway and subsequent immune evasion resulting in an increased anti-tumour immune response and cancer cell death. The recommended dose is 500mg, administered intravenously, once every three weeks for four cycles followed by 1,000mg once every six weeks thereafter. Treatment should continue until disease progression or unacceptable toxicity.

There is a lack of consensus on the standard of care for recurrent or advanced endometrial cancer in Irish clinical practice, with patients receiving a wide range of alternative chemotherapy regimens. Consequently, the Applicant included a range of treatments as the standard of care in the base case cost-effectiveness analysis. Pembrolizumab, as monotherapy and in combination with lenvatinib, has received marketing authorisation for the treatment of adults with dMMR or MSI-H advanced or recurrent endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. Pembrolizumab, as monotherapy and in combination with lenvatinib, may be comparators in the future, if reimbursed; this is not considered within this assessment.

1. Comparative effectiveness of dostarlimab (Jemperli®)

GARNET

The GARNET study is an on-going, phase I, open-label, multi-cohort trial. Cohort A1 enrolled adults, i.e., 18 years and above, with recurrent or advanced dMMR or MSI-H endometrial cancer, with disease progression on or after treatment with platinum doublet therapy. Data

from other cohorts are not presented here due to the inclusion of different indications to the current assessment. The clinical evidence that supports this assessment is thus derived from single-arm data.

Eligible individuals, in Cohort A1, received 500mg dostarlimab once every three weeks for four cycles, followed by 1,000mg once every six weeks thereafter. Individuals received treatment until disease progression or unacceptable toxicity or for a maximum of two years. Patients could continue to receive treatment beyond two years if the treating physician considered that the patient would continue to receive benefit. The primary endpoints were overall response rate (ORR) and duration of response (DOR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. Two populations from Cohort A1 are relevant to this assessment. The ITT population (which is analogous with the safety analysis set) and includes all patients that received at least one dose of dostarlimab (n=129). The efficacy population which includes individuals with at least 24 weeks follow-up to allow sufficient time to assess tumour response (n=105). Data from the ITT population informed the cost-effectiveness analysis.

Study results were presented for the March 2020 interim analysis; median duration of follow-up was 16.3 months. The primary efficacy endpoint results are available for the efficacy population only. ORR was 44.8% (95% CI 35.0 to 54.8). DOR was not reached. Median PFS for the ITT population was 5.6 months (95% CI 3.3 to 18.0), with median OS not reached. Inclusion criteria in the GARNET study are more restrictive than the licensed indication. To be eligible, patients must have received previous platinum *doublet* therapy and no more than two lines of anticancer therapy for recurrent or advanced disease. This limits the generalisability of the trial outcomes to Irish clinical practice. The open-label nature of this single-arm data and the immaturity of the survival data limit interpretation of the results and the conclusions that can be drawn.

Indirect comparative evidence

In the absence of direct head-to-head evidence, indirect comparative methods were required to inform the comparison of dostarlimab with standard of care. To address the

absence of robust comparator evidence and to provide a representation of standard of care, the Applicant conducted a real-world evidence (RWE) study using UK National Cancer Registry Analysis System (NCRAS) data. Data from this NCRAS RWE study and GARNET informed an unanchored matched-adjusted indirect comparison (MAIC). The outcomes defined in the MAIC were median PFS and OS. Results of the unanchored MAIC indicated that dostarlimab is associated with an OS benefit compared to standard of care. Due to the lack of PFS data in the NCRAS RWE study, a descriptive comparison was performed between time to next treatment from the NCRAS RWE study and PFS from GARNET. Although a greater proportion of individuals experienced disease progression initially with dostarlimab, a plateau was observed after six months, which was not observed with standard of care. The Review Group identified differences in study design, eligibility criteria and patient characteristics for GARNET and the NCRAS RWE, which cannot be easily adjusted for, as key limitations of the MAIC. The Review Group did not consider the MAIC outputs to be robust; results are highly uncertain and should be interpreted with caution.

A series of independent treatment comparisons were also conducted between dostarlimab and the individual chemotherapy regimens included in standard of care. These comparisons were associated with a high level of bias and uncertainty, and as such were included as supportive evidence only. Further details are not provided here.

2. Safety of dostarlimab (Jemperli®)

The safety population for GARNET included all individuals who received at least one dose of dostarlimab regardless of follow-up (n=129). Median treatment duration was 26.0 weeks. In the March 2020 data-cut, any grade, all-causality treatment emergent adverse events (TEAEs) were reported in 95.3% of individuals. The most common TEAEs were nausea (32.6%), diarrhoea (27.9%), anaemia (27.1%), fatigue (24.8%) and asthenia (21.7%). All-causality grade 3-4 TEAEs occurred in 48.1% of individuals. The most common grade 3 or above TEAEs were anaemia (14.7%) and abdominal pain (5.4%). Serious TEAEs were reported by 34.1% of individuals. The most common (occurring in greater than 2% of individuals) were abdominal pain (3.1%), acute kidney injury (3.1%), sepsis (3.1%), pulmonary embolism (2.3%), pyrexia (2.3%) and urinary tract infection (2.3%).

Overall, the available evidence suggests that dostarlimab safety is consistent with its pharmacological class and no new signals have been identified. However, uncertainties remain due to the limited size of the safety database, the lack of direct controls and lack of long-term data. To address the uncertainties, the Committee for Medicinal Products for Human Use requested that updated safety data from GARNET and data from a subsequent trial on dostarlimab be submitted.

3. Cost effectiveness of dostarlimab (Jemperli®)

Methods

A cost-utility analysis, using a partitioned survival model, with a cycle length of three weeks and a 40-year (lifetime) horizon, was submitted. A half cycle correction was applied. The model included three mutually exclusive health states: progression-free survival, post-progression survival and death. Standard parametric models were used to extrapolate PFS and OS data independently from GARNET and the NCRAS RWE study. PFS data for dostarlimab were based on the ITT population of GARNET. MAIC-adjusted OS data were used. A treatment-waning effect was applied to PFS and OS. It was assumed that waning would commence at 12 months after discontinuation of dostarlimab and would last for two years. The Review Group has concerns about the limited duration of follow-up in the GARNET trial and model-structural uncertainties (surrounding treatment cessation and duration of benefit). These limitations result in considerable uncertainty around the reliability of the outputs of the long-term modelling.

Utility data were derived from EQ-5D-5L data, from the GARNET study, mapped to EQ-5D-3L. Health state utility values were applied to the progression-free survival and post-progression survival health states regardless of treatment. Event specific utility values were included for grade 3 or above TEAEs. Adjustments were made for time-to-death and age.

Direct medical costs were included for drug acquisition (including administration), disease management, subsequent treatment, routine care and monitoring, diagnostic testing, end-of-life care and the management of TEAEs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group made several changes to the Applicant base case based on plausible alternative assumptions. These included using the OS data from the GARNET ITT population and excluding the time-to-death utility adjustment. The Applicant incremental cost-effectiveness ratio (ICER) and the NCPE-adjusted ICER are shown in Table 1.

Table1: Incremental cost-effectiveness results.

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis					
Dostarlimab	191,030	2.62			
Standard of care	30,305	0.98	160,725	1.64	97,812
NCPE-adjusted analysis					
Dostarlimab	188,498	2.48			
Standard of care	30,305	1.00	158,193	1.48	106,891

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

Mean probabilistic ICERS were aligned with the deterministic ICERs. Dostarlimab had a 0% probability of cost-effectiveness at both the €20,000 per QALY and €45,000 per QALY thresholds, for the Applicant and NCPE-adjusted base case.

In one-way sensitivity analysis, the main drivers of cost-effectiveness in both the Applicant and NCPE-adjusted base case were baseline, progression-free survival and post-progression survival health-state utility values. Scenario analyses indicated that the model was most sensitive to the choice of parametric model used to extrapolate OS data, the discount rate and assumptions surrounding treatment discontinuation and waning.

4. Budget impact of dostarlimab (Jemperli®)

The price-to-wholesaler of a 500mg vial of dostarlimab is €6,471.09. The annual per-patient drug acquisition cost of dostarlimab is €129,714.78 (€103,828.10 excluding VAT).

The Applicant used several sources to inform the eligible population estimates. These included the National Cancer Registry Ireland, clinical opinion, and the published literature. The Applicant assumed an initial market share of 50%, increasing to 70% in year five.

Including both incident and prevalent patients in year one and accounting for treatment discontinuation and deaths, the Applicant estimated that nine individuals would receive dostarlimab in year one decreasing to one patient in year five. The Applicant also presented a net drug budget impact assuming dostarlimab will displace current standard of care. The Review Group believes that the approach taken, by the Applicant, is likely to lead to an inaccurate estimate of the numbers of treated patients; the Review Group considers the values presented to be underestimates.

The Applicant estimated the cumulative five-year gross drug budget impact for dostarlimab to be €2.23 million (€1.79 million excluding VAT). The cumulative five-year net drug budget impact for dostarlimab was estimated to be €2.16 million (€1.73 million excluding VAT).

5. Patient submission.

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

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that dostarlimab 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.*