Cost-effectiveness of letermovir (Prevymis®) for the prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of letermovir (Prevymis®). Following assessment of the Applicant's submission, the NCPE recommends that letermovir (Prevymis®) 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) dossier on the cost effectiveness of letermovir (Prevymis®). 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 is 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 **May 2020**

Summary

In April 2019, Merck (the Applicant) submitted a dossier of clinical, safety and economic evidence for letermovir (Prevymis®) for the prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). Allogeneic HSCT recipients are immunocompromised, and are subsequently at increased risk for CMV reactivation and infection. In Ireland, a pre-emptive treatment (PET) approach is the current standard-of-care (SoC), based on regular virological monitoring and antiviral treatment when virus is detected. Antivirals currently used for PET include ganciclovir, valganciclovir and foscarnet. Letermovir is a novel direct-acting antiviral which works by inhibiting CMV DNA terminase complex required for cleavage and packaging of viral progeny DNA. Its efficacy has been established in tandem with regular CMV DNA monitoring and initiation of PET in cases of significant CMV DNAemia or disease. Letermovir is available in an oral and intravenous (IV) presentation and is administered at a dose of 480mg once daily, reduced to 240mg once daily if co-administered with ciclosporin. Prophylaxis with letermovir should continue through 100 days post-transplant. Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation. However, the safety and efficacy of letermovir use for more than 100 days has not been demonstrated.

1. Comparative effectiveness of letermovir

The clinical efficacy and safety of letermovir versus placebo was examined in one pivotal, randomised, double-blind, placebo-controlled Phase III trial in adult, CMV-R+ allogeneic HSCT recipients. 570 patients were randomised (2:1) to receive letermovir (n=376) at a dose of 480 mg once daily (adjusted to 240 mg once daily if co-administered with ciclosporin), or placebo (n=194). Letermovir was administered either orally or IV, at the discretion of the investigators. All patients received SoC, consisting of regular CMV DNA monitoring and initiation of CMV PET in cases of CMV viremia. Letermovir was discontinued in patients in whom PET was initiated. The primary efficacy endpoint of clinically significant CMV infection was defined by the incidence of CMV viremia warranting PET or the occurrence of CMV end-organ disease. Subjects had continued follow-up through Week 48

post-transplant. The median age was 54 years (range: 18 to 78 years). 50% of subjects received a myeloablative regimen, 52% were receiving ciclosporin. The most common primary reasons for transplant were acute myeloid leukaemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). At baseline, 31% of subjects were at high risk for CMV reactivation. 12% of patients had detectable CMV viral DNA at baseline. The primary analysis was conducted in patients with no detectable CMV DNA on Day 1 of treatment initiation. Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint. The proportion of subjects who failed prophylaxis by Week 24 was 37.5% in the letermovir group and 60.6% in the placebo group (treatment difference of -23.5% (95% CI, –32.5 to –14.6, p<0.0001)). The difference in the primary endpoint was primarily driven by a difference in the rate of initiating PET (16% letermovir vs 40% placebo). CMV end-organ disease occurred in 2% of patients in both groups. The benefits of avoiding PET include a potential reduction in the need for re-hospitalisation for IV ganciclovir, and a potential reduction in PET-related adverse events. However, the clinical trial did not provide any clear indication that letermovir prophylaxis will reduce the overall need of in-patient care compared to a SoC PET approach. There were no differences in the incidence of or time to engraftment between the letermovir and placebo groups. All-cause mortality was an exploratory endpoint, and was lower in the letermovir group though not statistically significantly different (23.8% vs 27.6%).

2. Safety of letermovir

The safety profile of letermovir prophylaxis is similar to that of present SoC with PET alone. The most commonly reported adverse reactions occurring in at least 1% of subjects in the letermovir group and at a frequency greater than placebo were: nausea (7.2%), diarrhoea (2.4%), and vomiting (1.9%). The most frequently reported adverse reactions that led to discontinuation of letermovir were nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%). The proportion of subjects with at least one serious adverse event reported was 44.2% in the letermovir group vs. 46.9% in the placebo group. The frequency of failure to engraft the transplant, and incidence/severity of graft-versus-host-disease (GVHD) were similar across arms.

3. Cost effectiveness of letermovir

Methods

The Applicant submitted a cost-utility analysis to assess the cost-effectiveness of letermovir compared to SoC alone, represented by the PET strategy employed in the clinical trial. The cost-effectiveness model consisted of a short-term decision-tree that reflected the clinical outcomes observed in the 48-week clinical trial, followed by a lifetime Markov model which reflected long-term survival, health-related-quality-of-life (HRQoL) and economic outcomes. Short-term model outcomes included: initiation of PET based on documented CMV viremia; CMV end-organ disease; CMV-related rehospitalisation; opportunistic infection, GVHD; and all-cause mortality. Treatment effects were based on data observed at week 14, week 24 and week 48 of the clinical trial. Long-term life expectancy was calculated by applying a relative risk to general population mortality, reflecting the increased long-term mortality risk expected in patients with the underlying health conditions observed in the clinical trial, and expected in clinical practice. Relative risks from a range of sources were applied by the Applicant. The NCPE Review Group considered that the most relevant source of mortality data was the unpublished ECO-CY-STEM study, a retrospective French cohort study funded by MSD, which assessed the association between CMV reactivation and overall mortality.

The primary health outcome of the model was the quality adjusted life year (QALY) as per national guidelines. Treatment-specific utilities were used for letermovir and SoC, derived from clinical trial EQ-5D data. The model included drug acquisition costs for letermovir and PET, CMV monitoring costs, PET administration costs, treatment costs for clinical outcomes and long-term survivor costs. The duration of letermovir treatment in the model was 69.4 days, in line with the mean duration of letermovir exposure recorded in the pivotal trial. However, in the clinical trial, there was an additional delay of approximately 10.9 days between trial participants receiving their transplant and initiation of letermovir treatment. This was due to a reluctance among investigators to initiate an investigational agent with potential toxicity prior to engraftment. Given the current knowledge of letermovir safety, this delay in starting letermovir is not expected to be observed in practice. The NCPE Review Group considered, therefore, that a duration of 80.3 days (69.4 days plus 10.9 days) is a more realistic reflection of expected clinical practice. A scenario in which it is assumed that

letermovir prophylaxis is continued for up to 200 days in a subset of patients at high risk for late CMV reactivation was conducted by the NCPE Review Group. This scenario reflects the statement in the SPC that extended prophylaxis may be of benefit. However the robustness of results in this scenario is limited by the lack of evidence of clinical efficacy, which was assumed to remain unchanged. In this scenario, costs of extended prophylaxis with letermovir and valganciclovir were added to the letermovir and SoC arms of the model, respectively. Costs and outcomes were discounted at an annual discount rate of 4%.

Results

The Review Group assessment identified a number of limitations in the Applicant's base case. These limitations were addressed in the NCPE Review Group adjusted base case with adjustments to the duration of letermovir prophylaxis, short- and long-term mortality assumptions and drug acquisition/administration costs. The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the Applicant's base case was €31,916/QALY. The ICER for the NCPE's adjusted base case varied from €50,305/QALY (assuming a mean duration of 80.3 days of letermovir, for standard prophylaxis), up to €71,524/QALY (assuming extended prophylaxis in patients at high risk). The ICER in the extended prophylaxis setting is highly uncertain given the absence of evidence for efficacy beyond 100 days. Using the NCPE adjusted base case, at a cost-effectiveness threshold of €20,000 and €45,000 per QALY, the probability of cost-effectiveness is 3.2% and 44.5% respectively, for standard prophylaxis. The main drivers of cost effectiveness in the model include the survival benefit at one year with letermovir, and the duration of letermovir prophylaxis.

4. Budget impact of letermovir

The Applicant applied for reimbursement under the High Tech Drug Arrangement for oral letermovir, and as a hospital-only product for IV letermovir. The price to wholesaler per tablet/vial of letermovir is: €162.50 (240mg tablet); €325.00 (480mg tablet); €178.60 (240mg vial). The total cost to the HSE per standard course of letermovir prophylaxis (assuming an average duration of 80.3 days), including wholesale mark-up, rebates and fees, is €19,315 per patient including VAT (assuming 50% of patients require IV letermovir for the first 14.1 days of treatment, and 60% of patients require 240mg letermovir due to

concomitant ciclosporin). Based on the current eligible population, the NCPE-adjusted projected cumulative net budget impact of letermovir over the first five years is approximately €2.8 million for standard prophylaxis, increasing to €4.5 million assuming some limited use of extended prophylaxis.

5. Patient submission

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

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that letermovir 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.