NCPE Assessment

Technical Summary

Tepotinib (Tepmetko®)

22025

29 November 2023

Applicant: Merck Serono Ltd

Tepotinib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tepotinib (Tepmetko®).

Following assessment of the Applicant's submission, the NCPE recommends that tepotinib (Tepmetko®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Merck Serono Ltd) Health Technology Assessment of tepotinib (Tepmetko®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.*

Summary

In January 2023, Merck Serono Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tepotinib (Tepmetko®) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. Current standard-of-care for this indication, in Ireland, generally includes chemotherapy, such as docetaxel (with or without nintedanib), gemcitabine or paclitaxel. The use of other immunotherapy comparators (i.e. atezolizumab and nivolumab) is very low for this indication (i.e. in the second-line setting). Merck Serono Ltd is seeking reimbursement of tepotinib (Tepmetko®) on the High Tech Drug Arrangement.

1. Comparative effectiveness of Tepotinib (Tepmetko®)

The efficacy and safety of tepotinib is investigated in the VISION trial, which is an ongoing Phase II, single-arm study that investigates tepotinib in patients with locally advanced or metastatic NSCLC harbouring METex14 skipping alterations or MET amplifications. Only those patients with METex14 skipping alterations, treated at second-line or later, are considered in the efficacy analysis. Tepotinib 450mg orally was taken once daily until disease progression, or due to withdrawal of consent, adverse event leading to discontinuation, or death. Data from the February 2022 data-cut informed the submission. Data from a more recent interim analysis (November 2022) was not available from the Applicant at the time of assessment. The primary efficacy endpoint is the Objective Response Rate (ORR) among patients who had undergone at least nine months of follow-up. Progression-Free Survival (PFS) and Overall Survival (OS) are secondary endpoints. The clinical efficacy population included 149 patients treated at second-line or later. The median age of patients was 70.8 years, 52.3% were female, and 55.7% were white. Almost all (95.3%) participants had metastatic disease at study entry. Platinum-based therapy was the most common prior treatment (86%) and 53% of patients had received immunotherapy. As of the February 2022 interim analysis, the ORR (by independent evaluation) was 45.0% (95% CI: 36.8% to 53.3%). The magnitude of this response is expected to provide benefit in the target patient population. The median PFS (by investigator assessment) and OS were 8.3 and 19.6 months,

respectively. However, in the absence of a randomised comparison, the impact on time-dependent endpoints, such as PFS and OS, cannot be isolated. The patient-reported outcome measurements, including quality-of-life assessments, generally remained unchanged throughout the study, though the absence of a control arm limits the conclusions that can be drawn from these results.

For the purposes of the comparative-effectiveness analysis, the Applicant selected docetaxel monotherapy, and docetaxel plus nintedanib as relevant comparators. There was insufficient evidence for a comparison with gemcitabine and paclitaxel. Other immunotherapy comparators (i.e atezolizumab and nivolumab) were not considered in the CEM, given their limited use at this stage of therapy. Comparative effectiveness of tepotinib relative to docetaxel monotherapy and docetaxel plus nintedanib, was informed by an unanchored matching-adjusted indirect comparison (MAIC). Individual-patient data from the VISION study was reweighted to match aggregate data from the LUME-lung-1 study (for the comparison of tepotinib with docetaxel plus nintedanib), and the REVEL study (for the comparison of tepotinib with docetaxel monotherapy). These comparator trials were conducted in the wildtype-NSCLC population, which is not the population of interest for this assessment. There were considerable differences between the characteristics of the VISION population cohort prior to and after reweighting. This resulted in a substantially reduced effective sample size, which considerably increased the uncertainty in the results. Differences in study design were also evident across the studies. Furthermore, the Review Group considered that important prognostic factors were not accounted for in the MAIC. While the results of the Applicant's unanchored MAIC indicated improvements in both OS and PFS compared with both comparators, the considerable limitations of the MAIC mean that the results are highly uncertain and should be interpreted with caution.

2. Safety of Tepotinib (Tepmetko®)

The most common adverse events (AEs) in the VISION trial were oedema (77.3%), peripheral oedema (65.6%), nausea (30.2%), hypalbuminaemia (28.5%), diarrhoea (27.8%), and an increase in creatinine (27.1%). The most common serious AEs, occurring in at least 1% of patients were peripheral oedema (3.1%), generalised oedema (2.1%) and interstitial lung

disease (1.4%). Treatment emergent AEs leading to death were observed in 12% of patients, in which disease progression was the most frequent cause of death (30.6%). The percentage of patients who had AEs leading to permanent treatment discontinuation was 23.7%. The percentage of patients who had AEs leading to dose reduction was 34.0%. There is no direct safety data for tepotinib versus the comparators.

3. Cost effectiveness of Tepotinib (Tepmetko®)

Methods

The analysis was conducted from the perspective of the Health Service Executive (HSE) in Ireland. The treatment effects captured by the three health-state partitioned survival model were the delay of disease progression and death. The key efficacy inputs were PFS and OS. Tepotinib treatment effects were informed by the unanchored MAIC. Comparator treatment effects were informed by digitised OS and PFS Kaplan-Meier data from published clinical trials for each treatment. Due to the limitations with the MAIC, the NCPE Review Group requested that the Applicant include unadjusted tepotinib PFS and OS data from the VISION trial in the model, with comparator efficacy informed by hazard ratios derived from the MAICs. Notwithstanding this change, no robust estimate of the relative treatment effect on PFS and OS, for tepotinib versus comparators, is available.

Treatment duration was modelled using parametric modelling of time-to-treatment discontinuation data from the VISION trial for tepotinib (mean tepotinib duration of 13.6 months), and from the mean trial duration in REVEL (for docetaxel monotherapy) and LUME Lung-1 (for docetaxel plus nintedanib). Utilities for the progression-free and progressed health states were obtained from the VISION trial data. Disutilities (for Grade ≥3 AEs with incidence of greater than 5% in either VISION or REVEL and LUME-Lung 1) were derived from the literature. The model included costs for drug acquisition and administration, disease monitoring, AEs and terminal care. The Review Group identified a number of limitations in the Applicant's cost-effectiveness model, which were addressed through changes in the NCPE-adjusted base case including: the use of unadjusted data from the VISION study and a hazard ratio from the MAIC; the use of alternative parametric curves for PFS, OS, and time-to-treatment discontinuation for tepotinib; a 100% relative dose intensity (RDI) for tepotinib;

changes to the costs associated with subsequent-treatments and terminal-care.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The probability of cost-effectiveness of tepotinib is presented in Table 3.

Table 1: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Docetaxel[b]					
Docetaxel	27,475	0.79	- €100,239	- 1.27	- 78,648
Tepotinib	127,714	2.06			
Docetaxel+nintedanib[c]					
Docetaxel + nintedanib	42,977	0.94	- 78,649	- 0.73	- 108,461
Tepotinib	121,626	1.67			

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
a Costs and outcomes are discounted at 4%. Figures in the table are rounded, and so calculations may not be directly replicable.
b Corresponding probabilistic ICER using 1,000 iterations = €65,695/QALY.
c Corresponding probabilistic ICER using 1,000 iterations = €105,342/QALY.

Table 2:NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Docetaxel[b]					
Docetaxel	19,513	0.60	- 112,167	- 0.74	- 152,045
Tepotinib	131,680	1.34			
Docetaxel+nintedanib[c]					
Docetaxel + nintedanib	37,875	0.95	- 93,805	- 0.39	- 239,257
Tepotinib	131,680	1.34			

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
a Costs and outcomes are discounted at 4%. Figures in the table are rounded, and so calculations may not be directly replicable.
b Corresponding probabilistic ICER using 1,000 iterations = €151,654/QALY.
c Corresponding probabilistic ICER using 1,000 iterations =€240,211/QALY.

For the Applicant base case, the probability of cost-effectiveness for tepotinib compared with docetaxel was 0% and 16.3% at the €20,000 and €45,000 per QALY thresholds respectively. For the comparison with docetaxel+nintedanib, the probability of cost-effectiveness for tepotinib was less than 1% at both the €20,000 and €45,000 per QALY thresholds. For the NCPE adjusted base case, the probability of cost-effectiveness for tepotinib compared with docetaxel and docetaxel+nintedanib was 0% at thresholds of €20,000 and €45,000 per QALY.

When compared to docetaxel or docetaxel and nintedanib, a 78.47% and 75.97% reduction in the price to wholesaler of tepotinib is required to achieve an ICER of €45,000/QALY. This increases to 94.86% (docetaxel) and 84.86% (docetaxel+nintedanib) to achieve an ICER of €20,000/QALY.

Additional scenario analyses were conducted by the NCPE, in which an alternative parametric distribution was used for time on treatment (€202,483 per QALY), a naïve comparison of treatment effects (derived from VISION, REVEL and LUME-Lung) was conducted (€246,966 per QALY), and the tepotinib RDI was reduced to 93.5% (€220,546 per QALY).

4. Budget impact of Tepotinib (Tepmetko®)

The price to wholesaler for tepotinib (60 tablets x 225mg) is €8,500. The cost of tepotinib (assuming 13.6 months of treatment) is €116,270 per patient. The cost of docetaxel monotherapy is €1,569 (assuming 2.8 months of treatment). The cost of docetaxel plus nintedanib is €18,731 (assuming five months of docetaxel treatment and 4.2 months of nintedanib treatment).

Many of the budget-impact model inputs are very uncertain and there is therefore considerable uncertainty associated with the budget impact estimates. The Applicant predicted that three patients will be treated in Year 1 rising to 16 patients in Year 5, resulting in a total of 40 patients receiving treatment over five years. The 5-year cumulative gross drug budget impact of tepotinib was estimated, by the Applicant, to be €4.3 million (VAT not applicable). The net drug budget impact was similar. The NCPE considered that the prevalence of METex14 skipping mutations was underestimated by the Applicant, and considered that a more plausible prevalence rate would result in a gross budget impact of €7.4 million, which could increase as the rate of METex14 testing increases over time.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that tepotinib 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.