Cost-effectiveness of atezolizumab (Tecentriq®) for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

The NCPE assessment of atezolizumab has demonstrated evidence of benefit in terms of overall survival (OS) and safety profile compared with docetaxel, although the size of the long-term OS gain is highly uncertain. There is a very low probability of cost-effectiveness and a high probability that the ICER exceeds the cost effectiveness thresholds for existing treatments. The NCPE recommend that atezolizumab should 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.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Roche Products Ireland Ltd.) economic dossier on the cost effectiveness of atezolizumab (Tecentriq®). 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 **September 2018**

Summary

In January 2018, Roche Products Ireland Ltd. submitted a dossier of clinical, safety and economic evidence in support of atezolizumab for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Final data submitted by the applicant was received in August 2018.

Atezolizumab is a humanised monoclonal antibody that directly binds to PD-L1 and provides dual blockade of PD-1 and B7.1 receptors. PD-L1 is expressed on both tumour cells and tumour infiltrating cells (TILs); binding of PD-L1 to PD-1 and B-7.1 receptors on T cells and antigen-presenting cells (APCs) suppresses cytotoxic T Cell activity and proliferation, and cytokine production allowing the tumour to escape immune defence mechanisms and proliferate. Disruption of PD-L1 and PD-1 interaction allows the immune system to mount a response against the tumour cells by potentiating T cell immune responses, including anti-tumour responses. Atezolizumab is administered by IV infusion. The first dose is given over 60 minutes, with subsequent doses administered over 30 minutes if tolerated. Atezolizumab is given at a fixed dose of 1200mg, every three weeks. Treatment continues until loss of clinical benefit or unmanageable toxicity.

1. Comparative effectiveness of atezolizumab

In the submission, the main comparator of interest was docetaxel chemotherapy. At the request of the NCPE, a comparison with nivolumab and pembrolizumab was also presented.

Relative efficacy outcomes for the comparison with docetaxel were derived from the OAK and POPLAR studies. The OAK study is a Phase III, multi-centre open-label RCT (n=1225). The POPLAR study is a Phase II, multi-centre open-label RCT (n=287). Patients were randomised on a 1:1 basis to either atezolizumab 1200mg every three weeks (Q3W) by IV infusion (OAK n=425; POPLAR n=144), or docetaxel 75mg/m^2 Q3W by IV infusion (OAK n=425; POPLAR n=143). In both trials, treatment with atezolizumab could continue until loss of clinical benefit as assessed by the investigator in the absence of unmanageable toxicity in line with pre-specified criteria; docetaxel was administered until disease progression. No crossover was allowed between study arms. Patients were recruited to both studies regardless of PD-L1 status, but PD-L1 status on tumour-infiltrating immune cells (ICs) was a stratification factor in both trials and was measured using the VENTANA PD-L1 (PS142) assay. Overall survival (OS) was a (co-)primary endpoint of both trials.

Both studies demonstrated that atezolizumab was associated with a statistically significant improvement in OS compared to docetaxel. The advantage for atezolizumab was consistent across most sub-groups with the exception of squamous patients, where no statistically significant improvement was seen in either trial. In both trials, higher levels of PD-L1 expression were associated with greater clinical efficacy; however statistically significant improvements in OS were seen in patients with PD-L1<1% in the OAK study. No improvements in progression free survival (PFS) or overall response rate (ORR) compared to docetaxel were seen. Evidence from the FIR and BIRCH studies was also reviewed as part of the evaluation.

Comparative efficacy with nintedanib, nivolumab and pembrolizumab was derived from a network meta-analysis (NMA) using the fractional polynomials method. The NCPE expressed concern there was significant uncertainty in the synthesis of relative treatment effects, due to heterogeneity between the included clinical trials in the measurement of PD-L1 and different durations of follow-up.

2. Safety of atezolizumab

Safety and tolerability was reviewed based on the OAK study and other details published in the EPAR. Adverse events (AEs) were reported in virtually all patients in both arms. The incidence of Grade 3-4 AEs was greater with docetaxel (54%) than atezolizumab (37%). The incidence of treatment-related AEs was also greater with docetaxel (86%) than atezolizumab (64%). There were similar rates of serious AEs in both arms. There was a higher incidence of AEs leading to treatment withdrawal (19% versus 8%) and leading to dose modification/interruption (36% versus 25%) with docetaxel.

In terms of AEs of any grade, the most commonly reported (with a frequency ≥20%) with atezolizumab were nausea and vomiting, fatigue, decreased appetite, cough and anaemia. In terms of Grade 3-4 treatment related AEs, fatigue, anaemia, nausea, diarrhoea, musculo-skeletal pain and pruritus were most common. AEs of special interest (AEOSIs) were defined in the treatment protocol. AEOSIs were reported in 22.8% docetaxel and 30.2% atezolizumab patients. The majority of these in the atezolizumab arm were Grade 1-2, with only 5.1% of Grade ≥3. The most commonly observed AEOSIs with atezolizumab were hepatic events (8.2%), endocrine events (5.6%, including hypothyroidism (3%)), and pulmonary events

(1.8%, including pneumonitis (1%) and interstitial lung disease (0.5%)). No grade 5 immune-mediated AEs were observed.

3. Cost effectiveness of atezolizumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from OAK for the comparison with docetaxel, and from the NMA for the comparison with nintedanib, nivolumab and pembrolizumab. Cost-effectiveness was investigated using a three health state model with a 20 year time horizon. The model simulates patients through three health states: 'Progression-Free', 'Progressive disease' and 'Death'. All health states are mutually exclusive, and death is the 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 AE frequency used in the model were derived from OAK.

Survival outcomes from OAK were extrapolated to the full time horizon of the model using parametric extrapolation. Costs for drug acquisition, administration and monitoring were included in the model. Treatment costs were modelled based on time to treatment discontinuation in OAK. Select AEs were captured in the model, by applying costs and utility decrements. In the model base case utilities were modelled by a combination of time-to-death and progression based methods.

Analyses presented in this summary document are based on the list prices of the interventions. The NCPE implemented a number of changes to the model. In the NCPE preferred base case, atezolizumab was associated with an ICER of €152,458/QALY versus docetaxel (incremental costs €60,710, incremental QALYs 0.4). In the applicant base case, the ICER for atezolizumab versus docetaxel was €104,504/QALY (incremental costs €62,928, incremental QALYs 0.58). In both the NCPE and the applicant base case, atezolizumab was associated with lower costs and lower QALYs compared to nivolumab and pembrolizumab. In a fully incremental analysis of the applicant and the NCPE preferred base cases, atezolizumab was extendedly dominated.

The probability of cost-effectiveness at a threshold of €20,000/QALY and at a threshold of €45,000/QALY was 0% in both the applicant and NCPE base cases.

4. Budget impact of atezolizumab

Atezolizumab is submitted for reimbursement under the hospital oncology drugs management system. The proposed ex-manufacturer price per 1200mg vial is €4,699.80. The reimbursement cost for a treatment course of 13.5 cycles for a patient is €57,404 excluding VAT and €74,550.65 including VAT. Based on the applicant estimate of the eligible population, uptake of immunotherapies (75%) and assuming 28-40% market share, the applicant estimate of projected gross budget impact of the drug acquisition over the first five years is €38.73 million including VAT. The net budget impact is €38.34 million including VAT, based on the applicant assumptions. These estimates are highly sensitive to treatment duration, treatment uptake, market share estimates and the number of eligible patients. The NCPE provided detailed scenario analyses on the proposed budget impact.

5. State if any patient submissions were received, and name submitting organisations.

No patient organisation submissions were received during this HTA.

6. Conclusion

The NCPE assessment of atezolizumab has demonstrated additional benefit in terms of a statistically significant improvement in OS and an improved safety profile compared with docetaxel, but the magnitude of this benefit in the long-term is uncertain. There is a low probability of cost-effectiveness and a high probability that the ICER exceeds the cost-effectiveness threshold for existing treatments. The NCPE recommends that atezolizumab 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.