NCPE Assessment

Technical Summary

Atezolizumab (Tecentriq®)

HTA 20036

July 2023

Applicant: Roche Products (Ireland) Ltd

Atezolizumab as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) with a high risk of recurrence whose tumours have PD-L1 expression on at least 50% of tumour cells and who do not have *EGFR* mutant or *ALK*-positive mutations.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of atezolizumab (Tecentriq®) for this indication. Following assessment of the Applicant's submission, the NCPE recommends that atezolizumab (Tecentriq®) should not be considered for reimbursement, for this indication, 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 (Roche Products [Ireland] Ltd.) Health Technology Assessment of atezolizumab. 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.

Summary

In December 2022, Roche Products (Ireland) Ltd submitted a dossier which investigated the comparative effectiveness, cost effectiveness and potential budget impact of atezolizumab (Tecentriq®) for adjuvant treatment of adult patients with non-small cell lung cancer (NSCLC) following complete resection and platinum-based chemotherapy with a high risk of recurrence whose tumours have PD-L1 expression on at least 50% of tumour cells (≥50% TC) and who do not have epidermal growth factor receptor (*EGFR)* mutant or anaplastic large-cell lymphoma kinase (*ALK)*-positive mutations. Reimbursement is sought under the Oncology Drugs Management System.

Atezolizumab is a humanised monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the programmed death-1 (PD-1) and B7-1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response. Atezolizumab is licensed for use, for this indication, as monotherapy. It is administered by intravenous infusion at a dose of 840mg once every two weeks, or 1,200mg once every three weeks, or 1,680mg once every four weeks. Treatment should be continued for one year unless disease recurrence or unacceptable toxicity.

The Applicant anticipates that atezolizumab will be used in line with its licensed indication (as stated above). The current standard of care for the treatment of this patient population in Ireland is best supportive care (BSC), which comprises routine surveillance to assess for disease recurrence.

1. Comparative effectiveness of atezolizumab

IMpower010 is an ongoing, phase III, open-label, randomised controlled trial designed to evaluate the safety and efficacy of atezolizumab versus routine surveillance (BSC) in adult patients with completely resected stage IB-IIIA NSCLC with a high risk of recurrence (N=1,005). The licensed population pertains to a subgroup of the intention-to-treat population, and includes patients with stage II-IIIA NCSLC whose tumours have PD-L1 expression on ≥50% TC, who do not have *EGFR* mutant or *ALK*-positive mutations (n=209). The analysis in this subgroup was conducted on a post-hoc basis at the request of the European Medicines Agency (EMA); the trial was not powered to detect differences in disease-free survival (DFS) or overall survival (OS) in this subgroup.

At the interim DFS analysis (data cut-off: 21 January 2021; median follow-up: 32 months), DFS data were immature (22.6% and 43.7% of the subgroup who had been randomised to atezolizumab and BSC, respectively, experienced a DFS event). Median DFS was not reached in the atezolizumab arm,

and was 37.3 months in the BSC arm (HR 0.49; 95% confidence interval [CI] 0.29, 0.81). At the interim OS analysis, survival data were immature. Median OS was not reached in either arm (HR 0.42; 95% CI 0.23, 0.78).

The Review Group considered the immaturity of the available efficacy data to be a major source of uncertainty regarding the comparative effectiveness of atezolizumab. It is not yet clear if atezolizumab will result in a long-term reduction in the risk of disease recurrence as compared to BSC, or if the DFS gains observed to date instead reflect a delay in the occurrence of DFS events. Additional analyses whereby data are available for the majority of the licensed population will reduce this uncertainty. Furthermore, OS data are immature. It is unclear if the early improvements in DFS observed to date in IMpower010 will translate to improvements in survival.

2. Safety of atezolizumab

The adverse events observed in IMpower010 were reflective of the known safety profile of atezolizumab, when used as monotherapy in the adjuvant setting. No new or unexpected safety issues were identified.

3. Cost effectiveness of atezolizumab

Methods

A *de novo* Markov model was used to investigate the cost effectiveness of atezolizumab. The model comprised five health states: 'Disease free survival', 'Locoregional recurrence', '1L [first-line] metastatic recurrence', '2L [second-line] metastatic recurrence' and the absorbing state 'Death'. Health state occupancy was determined by transition probabilities between states and general population mortality risks. DFS was modelled using treatment-specific, parametric distributions fitted to time-to-event data. OS was modelled indirectly; the effect of the intervention on survival was captured via the increased length of time spent in the 'Disease-free survival' health state.

Where transition probabilities applied in the model could not be informed by IMpower010 data, model inputs were sourced from the literature. Data sources were identified through a 'real-world evidence structured review', as opposed to a systematic literature review. The Review Group considered there to be an increased risk of bias in the Applicant's approach; relevant literature may have been omitted. Utility values were derived from the literature as health-related quality of life data were not collected in the IMpower010 trial.

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. These changes included: the use of pooled data (as opposed to treatment-specific data) from the IMpower010 trial to inform DFS event types; the application of a cure assumption beginning at five years (as opposed to beginning at two years); the use of utility values identified from the literature which were more appropriately aligned with the NCPE's preferred methodological approach; and calculating the cost of treatment with atezolizumab based on a maximum treatment of one year, as per the product licence.

The Review Group's main concern regarding the cost-effectiveness model was the use of immature DFS data to inform the basis of the analysis. The Applicant was required to identify and inform the model with external data from multiple sources; it was not always clear that the searches used to identify such data were performed in a systematic way. It is not possible for the Review Group to ascertain the direction or magnitude of such potential biases.

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.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	64,018	6.19	-	-	-
Atezolizumab[b]	101,167	7.96	37,150	1.77	21,004

BSC: best supportive care; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year

[a] Corresponding probabilistic ICER using 2,000 iterations =€21,693/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. A discount rate of 4% is applied to both costs and outcomes.

[b] A PAS is currently in place for atezolizumab, not presented here

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	68,277	5.75	-	-	-
Atezolizumab[b]	113,991	7.19	45,714	1.45	31,640

BSC: best supportive care; **ICER:** incremental cost effectiveness ratio; **QALY**: quality adjusted life year.

[a] Corresponding probabilistic ICER using 2,000 iterations =€33,077/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. A discount rate of 4% is applied to both costs and outcomes.

[b] A PAS is currently in place for atezolizumab, not presented here.

The probabilities of cost-effectiveness, for atezolizumab versus BSC, under the NCPE-adjusted base case were 20.9% at the €20,000/QALY and 72.9% at the €45,000/QALY. A price-ICER analysis conducted using the NCPE-adjusted base case indicated a 33.7% reduction in the price of atezolizumab was required to meet the €20,000/QALY threshold.

3. Budget impact of atezolizumab

The price to wholesaler for atezolizumab is €2,980.35 per 840mg vial, and €4,284.61 per 1,200mg vial. Value-added tax (VAT) is applicable. Treatment costs in the budget impact model assumed 66.7% of patients were treated with atezolizumab at a dose of 1,680mg once every four weeks, and the remainder received 1,200mg once every three weeks. The estimated total treatment cost per patient per year for atezolizumab is €89,224 (€71,340 excluding VAT) for those treated with 1,680mg once every four weeks, and €85,514 (€68,374 excluding VAT) for those treated with 1,200mg once every three weeks.

The eligible population is defined as patients with stage II-IIIA NSCLC, who have undergone surgical resection and received systemic chemotherapy, whose tumours have PD-L1 expression on ≥50% TC and do not have *EGFR* mutant or *ALK* positive mutations. Under the assumptions and model inputs applied by the Applicant, this resulted in an estimated total population of 25 patients per year eligible for treatment under the product licence in Year 1, increasing to 26 patients per year by Year 5. The NCPE-adjusted base case applied alternative model inputs to estimate the proportion of patients expected to undergo surgical resection and receive systemic chemotherapy; this resulted in an estimated total population of 37 patients per year eligible for treatment under the product licence in Year 1, increasing to 38 patients per year by Year 5.

The Applicant limited treatment duration to 48 weeks, based on the treatment protocol in IMpower010. The NCPE-adjusted base case assumes treatment duration will continue for one year, in line with the product licence.

The Applicant's five-year cumulative gross drug budget impact for atezolizumab was estimated at €10.2 million (€8.2 million excluding VAT). The NCPE-adjusted five-year cumulative gross drug budget impact for atezolizumab was €16.4 million (€13.1 million excluding VAT). It is not anticipated that reimbursement of atezolizumab would displace any other drugs, meaning the gross and net drug budget impact results are equivalent. The Applicant did not include any non-drug costs or cost offsets in the budget impact analysis.

4. Patient submission

A Patient Organisation Submission was received from the Irish Lung Cancer Community (ILCC).

5. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that atezolizumab (Tecentriq ®) 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.