Cost-effectiveness of alectinib (Alecensa®) for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung carcinoma (NSCLC)

The NCPE has issued a recommendation regarding the cost-effectiveness of alectinib (Alecensa®). Following assessment of the applicant's submission, the NCPE recommends that alectinib (Alecensa®) for the first line treatment of adult patients with ALK-positive advanced NSCLC 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 alectinib (Alecensa®). 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 **January 2019**

Summary

In December 2017 the EU Commission granted marketing authorisation for alectinib for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). At the same time, they also converted the conditional marketing authorisation to a standard marketing authorisation for the crizotinib failure indication (2L) which had been approved in the EU since February 2017. In April 2018, Roche Products (Ireland) Ltd submitted a dossier examining the cost-effectiveness of alectinib for the first-line treatment of ALK-positive advanced NSCLC.

The authorised dose for this indication is 600mg taken orally twice daily (total daily dose of 1200mg). Treatment should continue until disease progression or unacceptable toxicity. Alectinib is a highly selective CNS active ALK inhibitor.

Crizotinib and ceritinib were the chosen comparators in the cost-effectiveness analysis. This was considered appropriate by the NCPE.

1. **Comparative effectiveness of alectinib**

Direct evidence is available from the multi-centre, randomised, open-label, phase III, ALEX clinical trial comparing alectinib (600mg twice daily) with crizotinib (250mg twice daily) in patients with previously untreated, advanced ALK-positive NSCLC, including with asymptomatic CNS disease. The primary endpoint was progression-free survival determined by investigator using RECIST v1.1 or death from any cause (PFS-INV). Secondary endpoints included PFS measured by independent review committee (PFS-IRC), overall survival (OS), objective response rate (ORR), duration of response (DoR), time to CNS progression, safety and health-related quality of life (HRQoL) measures. The efficacy analysis is based on the ITT population (alectinib: N=152, crizotinib: N=151); with the February 2017 data-cut considered the primary analysis. More recent data from a December 2017 data-cut is also available.

At the February 2017 data-cut the median PFS-INV was not reached in the alectinib arm and was 11.1 months in the crizotinib arm (95% CI 9.1, 13.1); HR = 0.47 (95% CI 0.34, 0.65). At

the December 2017 data-cut the median PFS-INV was 34.8 months (95% CI 17.7, NE) in the alectinib arm and 10.9 months in the crizotinib arm (95% CI 9.1, 12.9); HR = 0.43 (95% CI 0.32, 0.58). Median OS was not reached in either arm at either data-cut; HR = 0.76 (95% CI 0.50, 1.15) at the December 2017 data-cut. The ORR (February 2017 data-cut) was 82.9% in the alectinib arm and 75.5% in the crizotinib arm. At the February 2017 data-cut, the time to CNS progression was significantly decreased with alectinib compared to crizotinib; (cause specific HR 0.16 [95% CI: 0.10, 0.28, p<0.0001]). At the December 2017 data-cut, patients who commenced the study with no CNS metastases at baseline had a median PFS of 34.8 months on alectinib, compared to 14.7 months on crizotinib (HR 0.47 [95% CI: 0.32, 0.71]). For patients that had CNS metastases at baseline, the median PFS was 27.7 months for alectinib compared to 7.4 months for crizotinib (HR 0.35 [95% CI: 0.22, 0.56]). HRQoL scores indicated similar patient reported QoL in both treatment arms. The NCPE review team has concerns regarding the immaturity of the OS data and potential confounding in OS due to subsequent treatments, resulting in uncertainty in the OS estimates.

In the absence of direct comparative evidence, an indirect treatment comparison was conducted via a network meta-analysis (NMA) to establish estimates of relative effectiveness of alectinib and ceritinib for use in the economic model. The NMA included three RCTs; ALEX (alectinib vs crizotinib), ASCEND-4 (ceritinib vs chemotherapy) and PROFILE 1014 (crizotinib vs. chemotherapy) as a bridging study. The NCPE review team recommends that any conclusions derived from the NMA should be interpreted with caution due to the following limitations which will affect the robustness of the survival results: (i) cross-over, which occurred in some of the trials, cannot be adjusted for in the NMA therefore there is a potential for confounding in OS data; (ii) there were differences in the chemotherapy comparator regimens used in the trials (iii) there were other differences within the three trials which may have affected the results of the NMA, i.e. in the ALEX trial approximately 40% of patients had CNS metastases at baseline, which is higher than the proportions observed in the other studies which was between 25% and 32%; (iv) the lack of maturity of the survival data (median OS was not observed for some treatment arms in the trials).

2. Safety of alectinib

Adverse events that occurred at a higher incidence in the ALEX trial with alectinib than with crizotinib were anaemia, myalgia and increased blood bilirubin. Adverse events that were more common with crizotinib included nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, ALT increased, AST increased and visual impairment. Serious adverse events reported in a higher proportion of patients in the alectinib arm than in the crizotinib arm (February 2017 data-cut) were lung infection (2% vs 0%) and acute kidney injury (3% vs 0%). All cases of lung infection were considered unrelated to the study treatment. Three quarters of the cases of acute kidney injury were judged to be related to treatment with alectinib. All three of these cases were resolved.

3. Cost effectiveness of alectinib

Methods

The cost-effectiveness model was a cost-utility partitioned survival (or AUC) Markov-model with a 30-year time horizon and cycle length of one week. The key effectiveness inputs in the model were OS and PFS. Clinical efficacy inputs for the crizotinib comparison were derived from the ALEX trial using the December 2017 data-cut. Clinical efficacy inputs for the alectinib versus ceritinib comparison were derived from the NMA. The model simulates patients through three mutually exclusive health states: progression-free survival, progressed disease and death. The model also distinguishes between patients who progress with CNS metastases and those who do not. Patients enter the model in the progression-free health state and can stay within the same state or move to progression or death at the end of each subsequent cycle. Patients with progression but no CNS progression can then subsequently progress into CNS progression or death. Death is an absorbing state. Each health state was assigned a specific cost and health utility. Utility values were derived from the ALEX trial for the progression-free and progressed disease health states. A utility for CNS-progressed patients was obtained from the literature. The same utilities were used regardless of treatment.

For the alectinib versus crizotinib comparison, survival outcomes from ALEX were extrapolated to the full time horizon of the model. Separate parametric models were fitted to each treatment arm. Several distributions were assessed and the most appropriate was

chosen. Alternative distributions were considered in sensitivity analyses. PFS of alectinib and crizotinib were aligned and overlapping for approximately the first 6-months of the ALEX trial before beginning to diverge, as visual fit of the survival curves was poor, the KM data was used up to 18-months, with an exponential tail added thereafter. For the alectinib versus ceritinib comparison, comparative efficacy was based on estimates from the NMA. HRs for PFS and OS were applied to parametric curves fit to the alectinib data from the ALEX trial.

All relevant costs were included in the model: including drug acquisition, monitoring, health state costs, post-progression treatments and CNS costs and costs of AEs. All costs were identified from Irish sources where possible.

The NCPE review team identified several key issues and uncertainties with the economic model. The model assumes a maintained treatment effect over time however scenario analyses applying differing assumptions result in large increases in the ICER. In addition, there is a high degree of uncertainty in the treatment sequence after progression, (as data was not systematically collected in the ALEX trial) and the optimal sequence to reflect Irish practice. Overall the NCPE review team has grave concerns that the cost-effectiveness model is associated with a high degree of uncertainty for both the crizotinib and ceritinib comparisons. There exists a large degree of spread on the incremental cost-effectiveness plane for both treatment comparisons with results frequently falling in the north west quadrant for the ceritinib comparison with alectinib associated with lower QALYs and higher costs.

Results

For the alectinib versus crizotinib comparison the applicant estimates an incremental cost of €79,813 for a gain of 1.36 QALYs, resulting in an ICER of €58,704 per QALY. For the alectinib versus ceritinib comparison the applicant estimates an incremental cost of €98,979 for a gain of 0.67 QALYs, resulting in an ICER of €146,721 per QALY.

Sensitivity analysis

The applicant presented a probabilistic sensitivity analysis (PSA) for each comparison. For the crizotinib comparison the PSA estimated an incremental cost of €81,047 for a gain of 1.33 QALYs, resulting in an ICER of €61,115 per QALY. For the alectinib versus ceritinib comparison the PSA estimates an incremental cost of €99,169 for a gain of 0.56 QALYs, resulting in an ICER of €178,358 per QALY. The probability of cost-effectiveness at willingness-to-pay thresholds of €45,000 and €20,000 per QALY was 19.9% and 0% respectively for the crizotinib comparison and 0.8% and 0% respectively for the ceritinib comparison. The applicant presented a variety of scenario analyses and performed appropriate sensitivity analyses. These analyses indicated that the model was particularly sensitive to the choice of OS curve, assumptions regarding duration of treatment effect, acquisition costs of alectinib and costs applied in the progressed disease health state. The ceritinib comparison was also sensitive to the HRs derived from the NMA.

4. **Budget impact of alectinib**

The price to wholesaler of alectinib is €5,579.11 for a pack of 224 150mg hard capsules. The annual acquisition cost per patient of alectinib, including all relevant mark-ups and rebates, is estimated at €75,298 with a total treatment cost of €218,365 based on an average treatment duration of 34.8 months from the ALEX trial.

The applicant estimates that there would be 10 eligible patients in year 1, rising to 17 in year 5. The projected gross budget impact including drug acquisition costs only and based on company estimates of market share was estimated as €752,984 (year 1), €1,957,759 (year 2), €3,237,831 (year 3), and €3,795,040 (years 4) and €3,855,278 (year 5), resulting in a cumulative budget impact of €13.6 million over 5-years.

The applicant provided separate net budget impacts of the incremental impact of including alectinib in preference to crizotinib and ceritinib. In the event of alectinib replacing crizotinib the 5-year cumulative net budget impact was €8.9M; in the event of alectinib replacing ceritinib the 5-year cumulative net budget impact was €6.9M.

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

No patient submissions were received during the course of this appraisal.

6. Conclusion

The NCPE recommends that alectinib for the first line treatment of ALK positive advanced NSCLC 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.