Cost effectiveness of crizotinib (Xalkori®) for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

The NCPE has issued a recommendation regarding the use of crizotinib in non-small cell lung cancer. The NCPE do not recommend reimbursement of crizotinib.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturers (Pfizer) economic dossier on the cost effectiveness of crizotinib (Xalkori®) for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). 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 examine 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 **August 2013**

Summary

1. In May 2013, Pfizer submitted a pharmacoeconomic evaluation and potential budget impact of crizotinib (Xalkori®) for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non small cell lung cancer (NSCLC). The company are seeking reimbursement under the High Tech drug scheme.

2. The economic evaluation presented compared crizotinib with chemotherapy (pemetrexed or docetaxel) in the indicated patient population. Due to its targeted nature, ALK-testing is required to identify eligible patients. The base case assumes routine ALK-testing regardless of the reimbursement of crizotinib.

3. The economic evaluation is predominantly based on safety and efficacy data from a comparative phase III trial (PROFILE 1007). The manufacturer also presented results from two one-armed trials (PROFILE 1001 (phase I) and PROFILE 1005 (phase II), which support the findings of the phase III trial.

   PROFILE 1007 is an ongoing, randomized, open-label study of crizotinib compared with chemotherapy in previously treated patients with advanced ALK-positive NSCLC (n=347). Patients in the chemotherapy arm received either pemetrexed or docetaxel. Upon progression, patients in the chemotherapy arm were permitted to cross over to PROFILE 1005 and receive crizotinib.

4. Crizotinib showed significant improvement in progression free survival (PFS), the primary endpoint of the study. Median PFS was 7.7 months in the crizotinib group vs. 3.0 months in the chemotherapy group.

   Objective response rate (ORR), defined as achieving either a partial or a complete response, was 65.3% (95% CI 57.7%, 72.4%) in the crizotinib arm compared to 19.5% (95% CI 13.9%, 26.2%) in the chemotherapy arm. Of these, only one patient in the crizotinib arm (<1%) achieved a complete response.

   An interim analysis of overall survival (OS) found no significant OS benefit of crizotinib. Estimated median OS for patients treated with crizotinib was 20.3 months compared to 22.8 months for patients treated with chemotherapy.

However, these estimates do not account for potential confounding due to crossover. A number of methodologies to adjust for crossover were proposed. Based on the method considered most appropriate by the Review Group, a hazard rate (HR) of 0.83 (95% CI 0.36,1.35) was estimated. OS is the main cause of uncertainty in the model. Data cut off for final OS analysis is projected to occur by the end of 2013.

EQ-5D data was collected at each cycle until progression. The overall score in the crizotinib arm was 0.82 (95% CI 0.79, 0.85), a significant improvement compared to chemotherapy (overall score 0.73).

Crizotinib has been generally safe and well tolerated by patients. Most common grade 3 and 4 adverse events were elevated transaminases (16%) and neutropenia (13%).

5. A Markov Model was developed in Microsoft Excel® to model the clinical and economic outcomes. It is a three health state model (progression free, progressive disease, death) and the model cycle length is 30 days. It is a lifetime model, which is set at 10 years.

   The probabilities of moving between health states 'progression free', 'progressive disease' and 'death' are derived from PROFILE 1007 using calibration of PFS and OS data.

6. Since trials are still ongoing, treatment effects on PFS and OS need to be extrapolated. The base case assumes a retained benefit, which means that accrued benefits on PFS and OS will be retained, but subsequent rates are the same for both arms. Extrapolation starts from 2 years onwards. Scenarios using more optimistic and more conservative approaches were also presented.

   The utility data (EQ-5D) collected in the trial is used in combination with utilities from the literature.

7. In the base case (assuming no additional cost due to ALK testing), crizotinib treatment for ALK-positive patients with previously treated advanced NSCLC results in an incremental cost of approximately €41,690 and a QALY gain of approximately 0.252. This yields an ICER of **€165,616/QALY**. Assuming

additional costs due to ALK testing in the crizotinib arm increases the ICER to **€185,798/QALY**.

8. The company presented a number of scenarios, a one way sensitivity analysis as well as a probabilistic analysis in order to explore uncertainty associated with the parameters.

   Alternative extrapolation assumptions results in ICERs in the range of €159,388/QALY to €296,631/QALY. One-way sensitivity analysis highlights that the model is highly sensitive to overall survival estimates, utility estimates and drug costs. ICERs vary between €120,384/QALY and €307,452/QALY.

   The probabilistic analysis indicates that at a threshold of €45,000/QALY, the probability of crizotinib being cost effective is 5%.

9. The monthly treatment cost of crizotinib is €6,457. Assuming treatment duration of 7.7 months (median PFS in PROFILE 1007) this equates to €49,719 per treatment course. Based on the National Cancer Registry, the projected number of patients treated with crizotinib will increase from 16 patients in 2013 to 36 patients in 2017. The gross budget impact is estimated to increase from €371,923 in 2013 to €1,610,893 in 2017; a cumulative 5 year gross budget impact of €6,280,855. Subtracting the cost of treatment alternatives forgone, the cumulative 5 year net budget impact is €5,111,605, increasing from €252,000 in 2013 to €1,341,066 in 2017.

   The cumulative cost of ALK-testing over the next 5 years is estimated to be in the range of €457,870 to €700,018.

10. Crizotinib is the first targeted therapy for adults with previously treated ALK-positive advanced NSCLC. Crizotinib has shown to result in improved quality of life until progression and prolonged progression free survival. At this time, there is no evidence to confirm an overall survival benefit.

    At its current price, the NCPE cannot recommend crizotinib as a cost-effective treatment option. We do not consider the health benefit to be sufficient to justify the proposed price.