Cost effectiveness of alpelisib (Piqray®) for the treatment of postmenopausal women, and men, with HR+, HER2-, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of alpelisib (Piqray®). Following assessment of the Applicant's submission, the NCPE recommends that alpelisib (Piqray®) not be considered for reimbursement. 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 NCPE to carry out an evaluation of the Applicant's (Novartis Pharmaceuticals) Health Technology Assessment dossier on alpelisib (Piqray®). 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 **December 2021**

Summary

In February 2021, Novartis Pharmaceuticals submitted a dossier investigating the clinical effectiveness, cost effectiveness and potential budget impact of alpelisib (Piqray®) for the treatment of postmenopausal women, and men, with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following endocrine therapy (ET) as monotherapy. Reimbursement is sought under the High Tech Drug Arrangement.

Alpelisib is a small molecule, α-specific class I phosphatidylinositol-3-kinase (PI3Kα) inhibitor. Patients should be selected for treatment based on the presence of a *PIK3CA* mutation in tumour or plasma specimens, using a validated test. The recommended dose of alpelisib is 300 mg taken orally once daily. Dose modifications may be necessary to improve tolerability, with dose reductions permitted to a maximum of two levels (250 mg once daily and 200 mg once daily). Alpelisib is given in combination with fulvestrant for this indication. Fulvestrant is administered intramuscularly at a dose of 500 mg on days 1 and 15 of cycle 1, and on day 1 of each one-month cycle thereafter. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

In line with the licence, the population eligible for alpelisib in combination with fulvestrant (herein, alpelisib plus fulvestrant) includes those treated with ET as monotherapy in the (neo)-adjuvant setting who progress to locally advanced or metastatic disease, and those who are diagnosed with *de novo* locally advanced or metastatic disease who are treated with, and progress on, ET as monotherapy. Comparators relevant to clinical practice in Ireland are ribociclib in combination with fulvestrant (ribociclib plus fulvestrant), palbociclib in combination with fulvestrant (palbociclib plus fulvestrant), and everolimus in combination with exemestane (everolimus plus exemestane). Abemaciclib in combination with fulvestrant (abemaciclib plus fulvestrant) is licensed but not reimbursed in Ireland, and was included as a comparator by the Applicant in a scenario analysis.

Of note, the efficacy of alpelisib in patients who have previously received CDK4/6 inhibitors (including ribociclib, palbociclib or abemaciclib) has not been established, and this population is not included in the licensed indication.

1. Comparative effectiveness of alpelisib

Direct comparative evidence

The pivotal trial supporting product registration was the SOLAR-1 trial. This was a phase III, randomised, double-blinded, placebo-controlled trial which evaluated the safety and efficacy of alpelisib plus fulvestrant, as compared to placebo in combination with fulvestrant (placebo plus fulvestrant), in adult patients with HR+, HER2-, locally advanced or metastatic breast cancer. The study recruited patients with both *PIK3CA*-mutated and wild-type disease (N=572), with randomisation stratified by *PIK3CA*-mutation status. As the marketing authorisation pertains to those with *PIK3CA* mutations, only results from the cohort with *PIK3CA*-mutated tumours are presented here (n=341). The primary endpoint was progression-free survival (PFS; local investigator-assessed) in the cohort with *PIK3CA*-mutated tumours. Overall survival (OS) was designated a key secondary endpoint. At the primary efficacy analysis (data cut-off June 2018), alpelisib plus fulvestrant was associated with an investigator-assessed PFS benefit versus placebo plus fulvestrant (median PFS 11.0 months versus 5.7 months, respectively; hazard ratio [HR] 0.65, 95% CI: 0.50, 0.85). No statistically significant OS benefit was demonstrated. At the final OS analysis (data cut-off April 2020), median OS in the alpelisib plus fulvestrant arm was 39.3 months versus 31.4 months in the placebo plus fulvestrant arm (HR 0.86, 95% CI: 0.64, 1.15).

Indirect comparative evidence

The Applicant undertook an indirect treatment comparison (ITC) for PFS and OS (using the Bucher method) to provide comparative evidence against ribociclib plus fulvestrant, palbociclib plus fulvestrant, abemaciclib plus fulvestrant (not currently reimbursed; presented in a scenario analysis), and everolimus plus exemestane. Due to paucity of data for the comparison to everolimus plus exemestane, it was necessary to relax population criteria to include studies of patients with advanced breast cancer regardless of *PIK3CA*-mutation and HER2 status.

The ITC results indicated that there were no statistically significantly differences in efficacy (for PFS and OS) between alpelisib plus fulvestrant and any of the comparators. Point estimates of the HRs of both OS and PFS were indicative of a treatment benefit of alpelisib plus fulvestrant versus everolimus plus exemestane, and similar efficacy versus ribociclib

plus fulvestrant (with a possible small OS benefit associated with alpelisib). Both abemaciclib and palbociclib demonstrated numerically superior OS and PFS compared with alpelisib plus fulvestrant, though the differences were small. Following assessment of the ITC, the Applicant elected to assume a 'class effect' for all CDK4/6 inhibitors, based on data for ribociclib (i.e. the efficacy of palbociclib and abemaciclib, in terms of PFS and OS, were assumed to equal that of ribociclib). The Applicant reported that this assumption was based on heterogeneity of studies included in the ITC, and that the study population for the trial relating to ribociclib (MONALEESA-3) was more closely aligned with the SOLAR-1 population than either of the palbociclib (PALOMA-3) or abemaciclib (MONARCH-2) trials. However, the Review Group noted key differences in study populations (e.g. methods used to assess *PIK3CA*-mutation status). Furthermore, no evidence of pre-specified criteria being used to inform this decision was provided, meaning the Review Group were concerned that the decision to use ribociclib plus fulvestrant to represent the class effect of CDK4/6 inhibitors may have been post-hoc and results driven.

2. Safety of alpelisib

The safety profile of alpelisib plus fulvestrant has been evaluated in the SOLAR-1 and BYLieve studies. The BYLieve study is a non-comparative, multi-cohort study with a study population that is not aligned with the licensed population; data were considered supportive for the purpose of the safety analysis. In the comparative SOLAR-1 trial, Grade 3/4 adverse events occurred more frequently in the alpelisib plus fulvestrant arm (76.1%), as compared to the placebo plus fulvestrant arm (35.5%). The most common adverse events associated with alpelisib include hyperglycemia, rash and gastrointestinal toxicity. In the SOLAR-1 trial, 57.4% of participants who received alpelisib required treatment for hyperglycemia. The majority of these patients were treated with oral agents, and hyperglycemia tended to resolve following discontinuation of alpelisib.

3. Cost effectiveness of alpelisib

The population in the cost-effectiveness analysis consisted of patients with HR+, HER2-, locally advanced or metastatic *PIK3CA*-mutated breast cancer who progressed following ET as monotherapy. This is aligned with the licenced indication in Ireland and corresponds to the *PIK3CA*-mutated subgroup of the pivotal SOLAR-1 trial. A partitioned survival model was

submitted by the Applicant, consisting of three mutually exclusive health states: Progression-Free Survival, Progressed Disease and Death. Survival curves were fit to the SOLAR-1 trial data and extrapolated over a lifetime horizon, with the relative treatment effects derived from the ITC applied to these curves to predict outcomes for comparators. Utilities used in the model were derived from EQ-5D 5L data collected during the SOLAR-1 trial, and mapped to EQ-5D 3L. Costs in the model included drug acquisition costs, *PIK3CA*-mutation testing costs, post-progression treatment costs, adverse events-related treatment costs, costs associated with monitoring and follow-up, and end-of-life care.

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Also included in Table 1 are the results for the scenario analysis comparing alpelisib plus fulvestrant to abemaciclib plus fulvestrant. Clinical opinion obtained by the Review Group indicated that ribociclib plus fulvestrant and palbociclib plus fulvestrant are the most relevant comparators in the licensed population in Ireland.

Table 1 Results of Applicant's base case deterministic cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Alpelisib plus fulvestrant	143,899	2.28			
Base case comparators					
Ribociclib plus fulvestrant	136,202	2.16	7,697	0.12	65,491
Palbociclib plus fulvestrant	117,607	2.16	26,291	0.12	223,712
Everolimus plus exemestane	115,044	1.93	28,855	0.35	83,280
Scenario analysis comparator					
Abemaciclib plus fulvestrant	129,089	2.16	14,810	0.12	126,018

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
Figures in the table are rounded, and so calculations will not be directly replicable. Discount rate of 4% applied to costs and outcomes.

The scatterplots of probabilistic sensitivity analysis (PSA) highlight that (versus all base case comparators), PSA iterations are spread across all quadrants of the cost effectiveness plane. Of particular note, much spread occurs into the 'less costly, less effective' quadrant. The probabilities of cost effectiveness at the €20,000/QALY and €45,000/QALY thresholds were defined by the Applicant as the proportion of PSA iterations with positive net monetary benefit (Table 2). Using this approach, iterations can be considered cost effective in spite of poorer health outcomes if costs are sufficiently reduced. However, the Review Group note that the payer thresholds cannot be assumed to be equivalent in this quadrant, therefore the probabilities of cost-effectiveness should be interpreted with caution.

Table 2 Probabilities of cost effectiveness of alpelisib plus fulvestrant vs. comparators

Comparator	Probability of cost effectiveness at €20,000/QALY threshold	Probability of cost effectiveness at €45,000/QALY threshold
Ribociclib plus fulvestrant	45%	49%
Palbociclib plus fulvestrant	15%	6%
Everolimus plus exemestane	16%	15%

QALY: quality-adjusted life year

Probabilities have been calculated under the assumption that interventions associated with a positive net monetary benefit are considered cost effective. This includes a proportion of iterations which are associated with an incremental reduction in both costs and QALYs.

The PSA indicates that, when compared to all base case comparators alpelisib plus fulvestrant may not improve, or may worsen, clinical outcomes. Thus the key issue underpinning this analysis is the uncertain anticipated clinical benefit in the licensed population. The Review Group identified a number of additional limitations and key uncertainties associated with the Applicant's base case. These include issues relating to the utility values for comparator treatments and for the Progressed Disease state, the calculation of drug costs, and the approach to deriving the cost of post-progression treatments. In many cases, there was a lack of robust, alternative data to inform these model parameters and assumptions.

4. Budget impact of alpelisib

Based on time-on-treatment data from the SOLAR-1 trial, the expected cost per treatment course of alpelisib plus fulvestrant is €54,022.87 (VAT not applicable). The Applicant projected a five-year cumulative gross drug budget impact of €10.5 million, a five-year cumulative net drug budget impact of €4.0 million, and a five-year cumulative net health budget impact of €4.2 million. The modelled population is aligned with the licensed population; if used in unlicensed populations (for example, in those with prior CDK4/6 inhibitor-based treatment), the budget impact would be higher.

5. Patient organisation submissions

No patient submissions were received.

6. Conclusion

The NCPE recommends that alpelisib not be considered for reimbursement*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.