



**Palbociclib (Ibrance<sup>®</sup>) for the treatment of hormone receptor positive, human epidermal growth factor receptor 2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy**

The NCPE has issued a recommendation regarding the cost-effectiveness of palbociclib (Ibrance<sup>®</sup>). Following NCPE assessment of the applicant's submission, palbociclib (Ibrance<sup>®</sup>) is not considered cost effective for this indication and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Pfizer Healthcare Ireland) economic dossier on the cost effectiveness of palbociclib (Ibrance<sup>®</sup>). 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.

## Summary

In December 2016, Pfizer Healthcare Ireland made a submission on palbociclib for the treatment of hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+/HER2-) locally advanced or metastatic breast cancer in combination with an aromatase inhibitor (first-line) or in combination with fulvestrant in women who have received prior endocrine therapy (second-line). Final correspondence from the applicant was received on 21st June 2017.

The licensed dose of palbociclib (as part of a combination regimen) for this indication is 125mg once daily for 21 consecutive days, followed by 7 days off treatment.

Pre/perimenopausal women should also be treated with a luteinizing hormone-releasing hormone agonist. The drug is to be dispensed in the community setting under the High Tech Scheme.

The base case comparator for the first-line evaluation is letrozole. Paclitaxel and capecitabine are considered in scenario analyses and tamoxifen is considered for the premenopausal population. In the second-line setting fulvestrant is evaluated in the base case; paclitaxel and capecitabine are considered in scenarios.

### 1. Comparative effectiveness of palbociclib

Evidence for treatment in the first-line setting was derived from the phase 2, open-label PALOMA-1 (overall survival) and the phase 3, double blind randomised clinical trial (RCT) PALOMA-2 (progression free survival). Both trials compared palbociclib + letrozole to letrozole + placebo. The double blind RCT, PALOMA-3 (palbociclib + fulvestrant vs. fulvestrant + placebo) provided evidence for treatment in the second-line setting. The drug is licensed without regard to menopausal status. The eligible populations of PALOMA-1 and PALOMA-2 were post-menopausal women with oestrogen receptor positive (ER+)/HER2- advanced breast cancer. In PALOMA-3, the eligible population were pre-, peri- and postmenopausal women with ER+/HER2- metastatic breast cancer. Therefore, efficacy in pre/perimenopausal patients has only been investigated in the second line setting. According to the license, treatment should be continued as long as the patient is deriving

clinical benefit from therapy or until unacceptable toxicity occurs. In PALOMA-1 and PALOMA-3, study treatment was continued until disease progression, unacceptable toxic effects, study withdrawal, or death. In PALOMA-2, patients could continue beyond progression. In all trials, the primary outcome was investigator-assessed progression free survival in the intention-to-treat population; secondary outcomes included overall survival. Along with other patient-reported outcome measurements, EQ-5D questionnaires were included in the PALOMA-2 and PALOMA-3 protocols.

In PALOMA-1, median progression free survival was 20.2 months (95%CI 13.8 - 27.5) with palbociclib + letrozole vs. 10.2 months (95%CI 5.7 - 12.6) with letrozole: HR 0.488 (95%CI 0.319 - 0.748);  $p = 0.0004$ . In PALOMA-2, median progression free survival was 24.8 months (95% CI 22.1 - not estimable) with palbociclib + letrozole vs. 14.5 months (95% CI, 12.9 - 17.1) with letrozole: HR = 0.58 (95% CI, 0.46 - 0.72);  $p < 0.001$ . In PALOMA-3, median progression free survival with palbociclib + fulvestrant was 11.2 months (95%CI 9.5 - 12.9) vs. 4.6 months (95%CI 3.5 - 5.6); HR= 0.497 (95%CI 0.398 - 0.620, one-sided  $p < 0.000001$ ). Overall survival data from all three trials were immature.

To inform model parameters for alternative comparators, separate network meta-analyses for progression free survival and overall survival were performed for both the first- and second-line treatment evaluations. Overall survival results from the network meta-analyses are inconclusive given the immaturity of pivotal trial data.

## **2. Safety of palbociclib**

In PALOMA-1, PALOMA-2 and PALOMA-3, safety was assessed in all patients who received at least one dose of study drug. In all, the most frequent palbociclib-associated adverse events were neutropenia and leukopenia.

## **3. Cost effectiveness of palbociclib**

The submission evaluates cost effectiveness separately for both the first-line and second-line populations. Partitioned survival Markov models with health states 'progression free', 'progressed disease' and 'death', are utilised. The time horizon was 15 years. The Review Group consider this time horizon to be too short for the first-line evaluation.

Treatment effects for progression free survival for the first-line and second-line evaluations were obtained from parametric survival curves fitted to Kaplan-Meier data from PALOMA-2 and PALOMA-3 respectively.

Due to the immaturity of the available overall survival data, extrapolation was problematic. For each model, four scenarios estimated overall survival benefit; some were based on unfounded assumptions, others on the immature data. The Review Group expressed concerns regarding all scenarios. Despite the immature data (which made even visual assessment of extrapolated survival curves extremely challenging), the Review Group considered the scenarios that involved parametric survival curves fitted to Kaplan-Meier data from PALOMA-1 and PALOMA-3 for the respective evaluations. Sensitivity analyses indicate that the parameters used to model overall survival are the highest drivers of uncertainty in both models. Extrapolated progression free survival data was used as a proxy for treatment duration for the intervention and comparator. Since treatment can continue beyond progression, the use of progression free survival data is likely to underestimate drug acquisition costs.

In the base case, the relative dose intensities for palbociclib + letrozole and palcociplib + fulvestrant (and respective comparator arms) were obtained from PALOMA-2 and PALOMA-3 respectively. Relative dose intensities of 100% are assumed for the indirect comparators. The model assumes that all pre- and perimenopausal patients will receive goserelin; in reality, not all will receive this drug.

Utility values for the first-line evaluation were derived directly or indirectly from PALOMA-2. On-treatment values for the second-line evaluation were derived from PALOMA-3. The first-line 'post-progressed' value was assumed to be appropriate for the second line evaluation. The on-treatment utility values for indirect comparators were derived from the literature.

Using the overall survival extrapolation scenario (which remains highly uncertain), the ICER in the first-line setting (vs. letrozole) is €217,312/QALY (incremental cost=€116,925, incremental QALY=0.538); zero probability of cost effectiveness at €45,000/QALY. The ICER

in the second-line setting (vs. fulvestrant) is €256,993/QALY (incremental cost =€63,306, incremental QALY=0.25); zero probability of cost effectiveness. The ICERs vs. the indirect comparators are based on unfounded assumptions pertaining to overall survival.

#### **4. Budget impact of palbociclib**

The price (to wholesaler) of palbociclib 125 mg (pack x 21) is €3,800. The total cost of palbociclib, to the HSE, per patient per year (assuming 100% dosing intensity, wholesale margin, rebate and High-Tech Patient Care Fee) is €51,564.89. This excludes the cost of co-prescribed drugs.

The eligible HR+/HER2- metastatic breast cancer population was estimated based on National Cancer Registry data and European literature sources. The applicant estimated that the market share for the first-line setting would increase from 20% (in Year 1) to 42% (in Year 5), and would decrease in the second-line setting from 35% to 18% over this period. Resultant predicted patient numbers are: first-line (80 (Year 1) increasing to 354 (Year 5)) and second-line (177 (Year 1) falling to 85 (Year 5)). The applicant's original base case model derived median (rather than mean) treatment durations from PALOMA-2 and PALOMA-3 respectively.

The gross budget impact for palbociclib is estimated to increase from €13.09 million in Year 1 to €17.63 million in Year 5; cumulative 5-year impact of €78.64 million. The net budget impact is estimated to increase from €11.25 million in Year 1 to €14.25 million in Year 5; cumulative 5-year impact of €66.82 million. This potential budget impact is likely to be underestimated.

#### **5. Patient Interest Group Submissions**

The Irish Cancer Society made a submission to the NCPE, in respect of palbociclib, on the 12th July 2017.

#### **6. Conclusion**

Following NCPE assessment of the applicant's submission, cost effectiveness of palbociclib (Ibrance®) for this indication has not been demonstrated, and therefore is not recommended for reimbursement.