Cost effectiveness of ribociclib (Kisqali®) in combination with an aromatase inhibitor for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy.

The NCPE has issued a recommendation regarding the cost-effectiveness of ribociclib (in combination with an aromatase inhibitor). Following assessment of the applicant's submission, the NCPE recommends that ribociclib (in combination with an aromatase inhibitor) 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 (Novartis Ireland) economic dossier on the cost effectiveness of ribociclib (in combination with an aromatase inhibitor). 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 **August 2018**

Summary

In February 2018, Novartis Ireland made a submission on ribociclib (Kisqali®) (in combination with an aromatase inhibitor) for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy. Final data required by the NCPE was received from the applicant on 19th July 2018. Comparators (and market share) were informed an applicant led advisory board.

1. Comparative effectiveness of ribociclib (in combination with an aromatase inhibitor)

Letrozole is considered a primary comparator. Evidence for ribociclib (in combination letrozole) compared to letrozole monotherapy was derived from the randomized, double-blind, placebo-controlled, phase III MONALESSA-2 trial. Eligible patients (n= 668) were randomised (1:1) to ribociclib (in combination with letrozole) or placebo (in combination with letrozole). Treatment could continue until disease progression, unacceptable toxicity, death or discontinuation. Dose reductions for ribociclib were permitted to manage adverse events. Crossover was not allowed. The primary end point was local investigator-assessed progression-free survival. Secondary end points included overall survival, independent review progression-free survival, objective response rate and safety. Efficacy analyses were performed in the intention-to-treat population.

At the first interim analysis (median follow-up 15.3 months), median progression free survival was not reached with ribociclib (in combination with letrozole) (95% CI, 19.3 to not reached) vs. 14.7 months (95% CI, 13.0 to 16.5) (HR = 0.56; 95% CI, 0.43 to 0.72). At the second interim analysis (median follow-up 26.4 months), median progression free survival was 25.3 months (95% CI: 23.0–30.3) vs. 16.0 months (95% CI: 13.4–18.2) in the respective arms (HR = 0.568 (95% CI 0.457 to 0.704)). Data for overall survival is immature; 24-month survival rates were 86.7% and 84.8% in the ribociclib (in combination with letrozole) and the placebo (in combination with letrozole) arms respectively.

Palbociclib (in combination with letrozole) is included as a second primary comparator. Additional comparators, palbociclib (in combination with fulvestrant), fulvestrant monotherapy, and chemotherapy (capecitabine or paclitaxel), are considered in scenarios.

Separate mixed treatment comparisons for progression free survival, objective response rate and overall survival were performed. Overall survival results were inconclusive given the immaturity of pivotal trial data.

2. Safety of ribociclib (in combination with an aromatase inhibitor)

In MONALESSA-2, safety was assessed in all patients who received at least one dose of study drug. At the first interim analysis, most patients experienced at least one adverse event (98.5% vs. 97.0% of the treatment and comparator arms respectively). Any grade adverse events occurring in over 35% of either arm were neutropenia, (74.3% vs. 5.2%), nausea (51.5% vs. 28.5%), infections (50.3% vs.42.4%), fatigue (36.5% vs. 30.0%), and diarrhoea (35.0% vs. 22.1%). The most common Grade ≥ 3 adverse events were neutropenia (59.3% vs. 0.9%), leukopenia (21.0% vs. 0.6%) and hypertension (9.9% vs. 10.9%). Infections were reported in 50.3% vs. 42.4% of the respective arms. Febrile neutropenia occurred in 1.5% of the treatment group. At the second interim analysis, no new or unexpected toxicities were observed. At least one adverse event was experienced in 99.1% vs. 97.6% of patients in the respective arms.

3. Cost effectiveness of ribociclib (in combination with an aromatase inhibitor)

Cost effectiveness was evaluated using a patient-level time-to-event simulation model with four health states: 'Progression Free Survival in first-line treatment (PFS1)', 'Progression Free Survival in second-line treatment (PFS2)', 'Progressed Disease (PD)' and 'Death'. For the comparison to letrozole monotherapy, treatment effects for 'PFS1' were obtained by exponential extrapolation of MONALESSA-2 Kaplan Meier data beyond 26.4 months. The Review Group's preferred base case is to use the Gompertz distribution here instead. For additional comparators, hazard ratios derived from the mixed treatment comparison were applied. 'PFS2' was modelled using data from the BOLERO-2 trial. The BOLERO-2 trial examined the addition of everolimus to exemestane in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer that had recurred or progressed following prior treatment with non-steroidal aromatase inhibitor. In the model, overall survival was modelled as a function of time spent in 'PFS1', 'PFS2' and 'PD'. The correlation between progression free survival/time to

progression and overall survival was evaluated using Pearson's product-moment correlation and Spearman's rank correlation. In the base case, the applicant applied a threshold of 5.5 months in PFS (i.e. no overall survival gain attributed to patients progressing before 5.5 months) with a proportion (0.78) of progression free survival gain translating into overall survival gain. Time to Treatment Discontinuation from MONALESSA-2 was also modelled, principally to provide modelling of the cost of drug administration.

The 'PFS1' state utility values were derived from MONALEESA-2. Utilities for the other states were derived from the literature. Disutilites associated with adverse events were not considered in the base case (apart from for chemotherapy in 'PFS1'). Disutilites were considered only in scenario analysis where the methodologies employed in their handling are likely to introduce much uncertainty.

Health state costs were informed by the advisory board. Costs associated with first and second line treatments were applied to the 'PFS1' and 'PFS2' states respectively. Costs associated with third and subsequent line treatments were applied to the 'PD' state. Costs associated with adverse events were applied only in 'PFS1'. An end of life cost was applied to all patients on entering the death state.

A number of changes to the model were implemented during the course of the NCPE evaluation. These included:

- base case utility values (from MONALEESA-2) were mapped from EQ-5D-5L to EQ-5D-3L
- base case utility values (from MONALEESA-2) were stratified by treatment arm and stratified by on- and off- treatment periods
- a number of revised drug acquisition costs and monitoring costs
- a number of revised sources and assumptions pertaining to adverse events

Cost-effectiveness outputs at the list price and also at a confidential discount were estimated. Only the outputs at list price are presented here.

With the Review Group's preferred base case (Gompertz extrapolation of 'PFS1' data), the incremental cost-effectiveness ratio (ICER) vs. letrozole is €220,591/QALY (incremental costs

€46,654/ incremental QALYs 0.21). Ribociclib (in combination with letrozole) is dominated by palbociclib (in combination with letrozole). The ICERs vs. the alternative comparators are: €296,351/QALY (€41,816/ 0.14) vs. fulvestrant, €5,706/QALY (€372/ 0.07) vs. palbociclib (in combination with fulvestrant) and €82,107/QALY (€51,928/ 0.63) vs. chemotherapy. All ICERs are sensitive to the confidential discount.

With the applicant's preferred base case (exponential extrapolation of 'PFS1' data), the ICER vs. letrozole is €108,019/QALY (€47,765/ 0.44); the probability of cost effectiveness at €45,000/QALY is zero. Ribociclib (in combination with letrozole) is dominated by palbociclib (in combination with letrozole); the probability of cost effectiveness is 22.4%. The ICERs for the alternative comparators are €140,320/QALY (€42,814/ 0.31) vs. fulvestrant, €881/QALY (€44/ 0.05) vs. palbociclib (in combination with fulvestrant) and €57,220/QALY (€52,650/ 0.92) vs. chemotherapy. All ICERs are sensitive to the confidential discount.

A scenario analysis that assumed 100% dose intensity was provided. This analysis assumes an exponential extrapolation of 'PFS1' data. Here, the ICER vs. letrozole increases from €108,019/QALY to €150,967/QALY. Palbociclib (in combination with letrozole) continues to dominate ribociclib (in combination with letrozole). The other ICERs are €202,562/QALY vs. fulvestrant, €380,687/QALY vs. palbociclib (in combination with fulvestrant) and €77,860/QALY vs. chemotherapy. All ICERs are sensitive to the confidential discount.

4. **Budget impact of ribociclib (in combination with letrozole)**

Budget impact outputs at the list price and also at a confidential discount were estimated. Only the outputs at list price are presented here.

The list price for the 63 x 200 mg pack is €3,628.29. Assuming 100% dose intensity, the annual drug acquisition cost (ribociclib) per patient (excluding patient care fee) would be €41,423.00 (inclusive of rebate).

The gross budget impact considers the drug acquisition cost of introducing ribociclib (in combination with letrozole) as a treatment option.

Under the applicant's assumptions, the gross budget impact of ribociclib (in combination with letrozole) is estimated to be €2.46 million in Year 1, €3.32 million in Year 2, €3.37 million in Year 3, €3.41 million in Year 4 and €3.46 million in Year 5; 5 year cumulative of about €16.02 million. The budget impact at 100% does intensity was also presented; the cumulative 5 year impact here is about €20.62 million.

Under the applicant's market share assumptions, the incremental drug acquisition cost is estimated to be €0.68 million in Year 1, €0.94 million in Year 2, €0.95 million in Year 3, €0.96 million in Year 4 and €0.98 million in Year 5; 5 year cumulative of about €4.51 million. When 100% does intensities are assumed for all drugs and a wastage cost attributed to palbociclib is removed, the 5 year cumulative impact is about €9.13 million. This incremental budget impact assumes that the most expensive comparator (palbociclib in combination with fulvestrant) commands 25% of the market share. This is not a licensed treatment option for the first-line setting. Thus, we caution the interpretation of this incremental impact.

5. Patient submission

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

6. Conclusion

Following NCPE assessment of the company submission, the NCPE recommends that ribociclib (in combination with an aromatase inhibitor) for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2 negative locally advanced or metastatic breast cancer as initial endocrine-based therapy, 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.