**Cost-effectiveness of neratinib (Nerlynx®) as extended adjuvant treatment of adults with early-stage HR+, HER2-overexpressed/amplified breast cancer who completed adjuvant trastuzumab-based therapy**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of neratinib (Nerlynx®). Following assessment of the Applicant's submission, the NCPE recommends that neratinib (Nerlynx®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Pierre Faber Ltd) economic dossier on the cost effectiveness of neratinib (Nerlynx ®). 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.

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

**National Centre for Pharmacoeconomics** **May 2021**

**Summary**

In July 2020, Pierre Faber Ltd submitted a dossier which investigated the cost-effectiveness of neratinib as extended adjuvant treatment of adults with early-stage hormone receptor positive (HR+), HER2-overexpressed/amplified breast cancer who have completed adjuvant trastuzumab-based therapy less than one year previously. Neratinib was approved by the EMA for this indication following re-examination of the submitted evidence after an initial negative opinion. The negative opinion was based on the overall ITT (intention-to-treat) HER2+ population from the pivotal ExteNET trial and was given on the basis that a clinically relevant benefit on the primary endpoint had not been established with an acceptable degree of certainty, and concerns due to substantial gastrointestinal toxicity, specifically diarrhoea. Neratinib was granted European marketing authorisation for the restricted indication. The marketing authorisation was based on an exploratory sub-group analysis of the HER2+ population, of patients with HR+ cancer who had completed trastuzumab-based therapy within one year of randomisation. Hereafter this sub-group will be referred to as the EMA label population. Neratinib is a protein kinase inhibitor.

The recommended dose of neratinib is 240mg (six 40mg tablets) taken orally, once daily continuously for one year. Patients should initiate treatment within one year following completion of trastuzumab-based therapy. The Applicant is seeking reimbursement under the High Tech Arrangement. The treatment landscape for early-stage HR+/HER2+ breast cancer is constantly and rapidly evolving such that appropriate comparators, and the place in the therapeutic pathway of neratinib are likely to change in the near future. There is no other licensed treatment for the extended adjuvant treatment of adults with early-stage HR+/HER2+ breast cancer, consequently the comparator here is 'no active comparator'. Pertuzumab in combination with trastuzumab and chemotherapy has recently been reimbursed in the neoadjuvant setting. ESMO guidelines and NICE recommend restriction of the use of neratinib to patients who have not received treatment with a HER2-directed treatment (i.e. pertuzumab), other than trastuzumab. If the ESMO guidelines are followed, patients receiving neoadjuvant pertuzumab would not be eligible for treatment with neratinib. Given that pertuzumab and trastuzumab emtansine have also recently been

assessed by the NCPE in the adjuvant and early stages of breast cancer, respectively, treatment pathways including these treatments could also be potential comparators in the future to adjuvant trastuzumab monotherapy followed by neratinib. However, these potential comparators have not been considered here.

## 1. Comparative effectiveness of neratinib (Nerlynx®)

Direct comparative evidence for the effectiveness of neratinib versus placebo (equivalent to 'no active comparator') is available from the ExteNET trial. ExteNET is an ongoing, three-part, randomised, double-blind, placebo-controlled, phase III trial comparing extended adjuvant therapy with neratinib versus placebo in women with early stage HER2+ breast cancer, who had received loco-regional surgery and/or radiotherapy, as well as standard of care chemotherapy and trastuzumab-based therapy. Patients who had received prior therapy with an HER1 and/or HER2 inhibitor, other than trastuzumab, were excluded from participation.

Eligible patients were randomly assigned (1:1) to either neratinib 240mg once per day or matching placebo. Treatment was administered continuously for 12 months. The primary endpoint was invasive disease-free survival (iDFS) at two years. Secondary endpoints included iDFS, time to distant recurrence (TTDR), distant DFS (DDFS), overall survival (OS) and safety. Health-related quality of life (HRQoL), was an exploratory endpoint, using the EQ-5D-3L and FACT-B questionnaires. Efficacy analyses were planned at two and five years after randomisation. Approximately 75% of patients reconsented for extended follow-up beyond two years. Median follow-up, in the EMA label population, was approximately 24 months for the two-year analysis and 62.5 months for the five-year analysis.

As the current reimbursement request is for the EMA label population, only these results are presented. Two-year iDFS was 95.3% in patients receiving neratinib and 90.9% in patients receiving placebo; hazard ratio (HR) = 0.50 (95% CI 0.31 to 0.78). Five-year iDFS was 90.4% in patients receiving neratinib and 85.8% in patients receiving placebo; HR = 0.61 (95% CI 0.43 to 0.85). Five-year DDFS was 92.1% in patients receiving neratinib and 87.8% in patients receiving placebo; hazard ratio (HR) = 0.60 (95% CI 0.41 to 0.87). OS results, after a median follow-up of eight years, indicate that 7.9% of patients in the neratinib group and

10.2% in the placebo group had died: HR = 0.79 (95% CI, 0.55 to 1.13). HRQoL differences between neratinib and placebo did not cross clinically meaningful thresholds.

There are concerns regarding the external validity of the ExteNET trial given the evolving treatment landscape and the exclusion of patients having received prior pertuzumab, bias introduced by multiple protocol amendments, the use of a subgroup of the ITT population and whether early gains in iDFS will translate into improvements in survival.

## 2. Safety of neratinib (Nerlynx®)

The safety population included all patients who had received at least one dose of study drug. Results for the EMA label population are presented and are consistent with the ITT population. Median duration of treatment was 11.5 months in patients receiving neratinib and 11.9 months in patients receiving placebo.

Treatment emergent adverse events (TEAEs) were more common in patients receiving neratinib (any 98.0%; grades 3-4 49.6%) compared to those receiving placebo (any 86.4%; grades 3-4 11.8%). More TEAEs lead to treatment discontinuation and dose reduction in patients receiving neratinib (27.0% and 30.9%, respectively) than in patients receiving placebo (5.0% and 2.1%, respectively). Diarrhoea was the most common TEAE with neratinib (grade 1-2 54.8%; grade 3 39.8%) compared to placebo (grade 1-2 32.5%; grade 3; 1.1%). In general, grade 3 diarrhoea occurred in the first month of treatment and was self-limiting. Other common TEAEs observed in the neratinib arm included nausea (43.8%, compared to 20.9% with placebo), fatigue (28.7% versus 20%), vomiting (26.3% versus 6.5%) and abdominal pain (23.6% versus 9.1%).

Diarrhoea is an expected side effect of neratinib, with grade 3 events occurring at an appreciable level in the ExteNET trial. Therefore, it is recommended that patients should be instructed to initiate prophylactic treatment with an antidiarrhoeal medicinal product with the first dose of neratinib and maintain regular dosing of the antidiarrhoeal medicinal product during the first one to two months of neratinib treatment.

## 3. Cost effectiveness of neratinib (Nerlynx®)

*Methods*

The cost-effectiveness of neratinib was assessed using a five health-state Markov cost-utility model with a cycle length of one month and a life-time horizon of 55 years. Patients enter the model in the iDFS health state and are treated with neratinib or given 'no active comparator' (placebo). Patients remain in the iDFS health state until they experience an invasive disease event, either local or distant recurrence, or death. After local recurrence, patients enter a tunnel health state for 12 months in which they receive adjuvant therapy before they transition to either remission or death. For patients with locally recurrent disease who transition to remission, the model assumes that all patients progress over time to distant recurrence or death. Costs and health-related utilities were allocated to each health state to calculate the weighted costs and QALYs per cycle.

Clinical data for iDFS, local and distant recurrence, remission rates and post-distant recurrence survival (PDRS) were derived directly from the EMA label population from the ExteNET trial. A transition probability from remission to distant recurrence was obtained from the literature. Utility values for the iDFS and remission health state were derived from the ExteNET trial. Utilities for local and distant recurrence were obtained from the literature. The same utilities were used in both arms. Disutilities were also included for adverse events including diarrhoea, and for advancing age. The Review Group considers that relevant costs were included in the model. Costs were included for active treatment, endocrine therapy in both arms, routine care and monitoring, diarrhoea prophylaxis, subsequent therapies, and adverse events. No additional treatment costs were included for 'no active treatment'. Irish cost data were used where possible.

*Results*

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested changes to the Applicant base case based on plausible alternatives. These included assuming 100% neratinib dose intensity, using the stratified gamma survival function for iDFS based on non-proportional hazards, a tapered treatment effect and using a different utility for distant recurrence. The NCPE adjusted ICERs and the Applicant ICERs are shown (Table 1).

**Table 1: Cost-effectiveness results*(versus 'no active treatment').**

| Treatment | Incremental costs (€) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|
| NCPE adjusted base case | 27,384 | 0.49 | 56,275 |
| Applicant base case | 15,739 | 0.68 | 23,014 |

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

An additional scenario was performed by the Review Group which assumes benefit (efficacy) stops in line with the ExteNET trial data. An ICER of €72,431 per QALY was obtained using this assumption in the NCPE adjusted base case and €57,070 with the Applicant base case assumptions.

The probability of neratinib being cost effective versus placebo (equivalent to 'no active treatment') was 7% and 32% at thresholds of €20,000 per QALY and €45,000 per QALY respectively, using the NCPE adjusted base case.

Deterministic sensitivity analyses indicated the NCPE adjusted base case was most sensitive to assumptions surrounding disease-free utility, neratinib treatment duration and dose intensity, time horizon, discount rate, and the inclusion of diarrhoea prophylaxis. Overall, the Review Group has concerns that the uncertainty in the incremental clinical benefit of neratinib, predominantly due to the use of a subgroup of the ITT population and concerns as to whether early gains in iDFS will translate into improvements in survival, leads to a lack of confidence in the cost-effectiveness estimates.

## 4. Budget impact of neratinib (Nerlynx®)

The price to wholesaler of neratinib is €5,101 for a pack of 180 x 40mg tablets. The mean 12-month drug acquisition cost per patient of neratinib, including all relevant fees, mark-ups and rebates is estimated as €63,489 (assuming a 100% dosing intensity). The Applicant's model assumed dosing intensity and mean treatment duration based on the ExteNET trial, resulting in an average treatment cost per patient of €37,624.

The Applicant estimated that 11 patients would be treated with neratinib in year 1, rising to 100 in year 5. The projected cumulative five-year gross budget impact is €8.9 million.

The Applicant provided a net budget impact including additional monitoring costs for neratinib, the cost of diarrhoea prophylaxis and the incremental cost of AEs compared to placebo. Cost-offsets were also included for patients avoiding disease recurrence. In this instance the cumulative five-year net budget impact is €8.4 million.

## 5. Patient submissions

No patient submissions were received in support of the application.

## 6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that neratinib (Nerlynx®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

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