Cost effectiveness of talazoparib (Talzenna®) for the treatment of adult patients with germline BRCA1/2-mutated, HER2-negative locally advanced or metastatic breast cancer.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of talazoparib (Talzenna®)**.** Following assessment of the Applicant's submission, the NCPE recommends that talazoparib (Talzenna®) 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 NCPE to carry out an assessment of the Applicant's (Pfizer Healthcare Ireland) economic dossier on the cost effectiveness of talazoparib (Talzenna®). 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 **September 2020**

Summary

In March 2020, Pfizer Healthcare Ireland submitted a dossier of clinical, safety and economic evidence in support of talazoparib for the treatment of adult patients with germline BRCA1-mutated (gBRCA1m) or germline BRCA2-mutated (gBRCAm2), HER2-negative (HER2-) locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. HER2- breast cancer comprises two subtypes: HER2-/hormone receptor-positive (HER2-/HR+) and triple negative breast cancer (TNBC). Patients with HR+ breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

Talazoparib is an inhibitor of PARP enzymes (PARPi), PARP1 and PARP2. PARPi therapies exert cytotoxic effects on cancer cells by two mechanisms; inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription; resulting in apoptosis and cell death. Talazoparib is the first PARPi to be assessed by the NCPE for the indication in question and the second gBRCAm-targeted (both gBRCA1m and gBRCA2m) therapy to receive European marketing authorisation for this indication. Patients should be selected for treatment based on the presence of deleterious or suspected deleterious gBRCAm determined by an experienced laboratory using a validated test method. Talazoparib is formulated as a hard capsule and is administered orally at a dose of 1mg daily. It should be administered until disease progression or unacceptable toxicity occurs. Dose interruptions or reductions based on severity and clinical presentation of adverse events (AEs) are permitted.

It is anticipated that talazoparib will be used as second- or third-line treatment in patients with HER2-/HR+ disease and as first- or second-line treatment in patients with TNBC. Standard of care in these lines of therapy include capecitabine, eribulin, gemcitabine and vinorelbine. Carboplatin-based regimens (monotherapy or in combination with gemcitabine) are also frequently prescribed for patients with TNBC or patients with HER2-/HR+ endocrine-resistant disease whose gBRCAm status is known. All relevant comparators have been included in the assessment. Olaparib is currently the only other PARPi and gBRCAm-

targeted therapy licensed in Europe for the indication in question. An analysis versus olaparib was also presented; however, it is not currently reimbursed in the Irish healthcare setting for this indication and is not considered standard of care.

1. Comparative effectiveness of talazoparib

Clinical evidence for talazoparib came from a phase III, open-label, randomised, parallel, two-arm, multi-centre study: EMBRACA. A total of 431 patients were enrolled and randomised (2:1) to receive either talazoparib administered at a dose of 1mg orally daily or physician's choice of single-agent chemotherapy (PCT). PCT was determined prior to randomisation for each patient and included one of the following:

- capecitabine
- eribulin mesylate
- gemcitabine
- vinorelbine.

All therapies were administered in repeated 21-day cycles until disease progression or unacceptable toxicity.

The primary endpoint was radiographic progression-free survival (PFS), determined by independent radiology facility assessment. Secondary endpoints were investigator assessed and included: objective response rate, overall survival (OS), and safety. Health-related quality of life was assessed as an exploratory endpoint.

The intention to treat (ITT) analysis included 287 patients randomised to talazoparib and 144 randomised to PCT (55 (43.7%) receiving capecitabine, 50 (39.7%) receiving eribulin, 12 (9.5%) receiving gemcitabine, and 9 (7.1%) receiving vinorelbine). The proportion of patients in the overall population with HR+ breast cancer was 55.9% (gBRCA1m 22%; gBRCA2m 78%), and with TNBC was 44.1% (gBRCA1m 75%; gBRCA2m 25%).

Marketing authorisation was based on an interim analysis of data (September 2017 data cut), with a median follow up of 11.2 months. A statistically significant improvement in PFS was demonstrated for talazoparib compared with PCT (median PFS 8.6 months vs 5.6

months; HR 0.54; 95% CI 0.41 to 0.71; p<0.001). PFS data at this cut-off point were fully mature. Data for the secondary endpoint of OS were immature at the time of the interim analysis, demonstrating a median of 22.3 months (95% CI 18.1 to 26.2) in the talazoparib arm and 19.5 months (95% CI 16.3 to 22.4) in the PCT arm (HR 0.76; 95% CI 0.55 to 1.06; p=0.11). An updated OS analysis was also presented, based on the final data cut of EMBRACA (September 2019). The final OS analysis also indicated that there was no significant difference observed between the talazoparib and PCT arms. Treatment with talazoparib resulted in a median OS of 19.3 months (95% CI 16.6 to 22.5), while patients in the PCT arm had a median OS of 19.5 months (95% CI 17.4 to 22.4) (HR 0.85; 95% CI 0.67 to 1.07; p=0.17). Results of the final data cut also indicated that patients receiving talazoparib had a statistically significant improvement in the global health scale/quality of life, as measured by the EORTC QLQ-C30, when compared to patients in the PCT arm.

In the absence of direct comparative evidence of talazoparib versus other comparators of interest including carboplatin, carboplatin in combination with gemcitabine, and olaparib, indirect treatment comparison (ITC) methods were explored. For the comparison with carboplatin (TNT trial; docetaxel versus carboplatin), neither an adjusted ITC nor a matching-adjusted indirect comparison (MAIC) were feasible due to the absence of a common comparator arm and insufficient reporting of patient characteristics, respectively. A naive comparison was therefore conducted. Results of this comparison suggested that talazoparib and carboplatin had similar PFS outcomes; OS data were not available for carboplatin. The Review Group highlighted that these results were highly uncertain, owing mainly to differences in trial populations. An adjusted ITC and MAIC were presented for the comparison of talazoparib and olaparib, using data from the EMBRACA and OlympiAD (olaparib versus PCT) trials. Results from the ITC were considered more robust than the MAIC, though still uncertain due to heterogeneity in the trial populations. Results of the ITC indicated that there was no statistically significant difference between olaparib and talazoparib for the outcomes of interest (PFS and OS).

2. Safety of talazoparib

The safety profile of talazoparib in the EMBRACA trial was characterised mainly by myelosuppression consisting of anaemia, leukopenia, neutropenia, and thrombocytopenia.

Anaemia was the most frequently reported AE experienced by patients in the talazoparib arm, with 38.8% of patients experiencing anaemia of grade 3-4 severity. Myelosuppression-associated AEs were considered to be manageable with appropriate risk minimisation measures, including dose modification and supportive care. Other frequently reported AEs included fatigue (50.3%), nausea (48.6%), headache (32.5%), and alopecia (25.2%). These AEs were generally of grade 1-2 severity.

3. Cost effectiveness of talazoparib

For the cost-effectiveness analysis, the key effectiveness inputs were OS and PFS. Clinical efficacy inputs for talazoparib and PCT, carboplatin, and olaparib were derived from their respective trials; EMBRACA, TNT, and OlympiAD. Cost effectiveness was based on a cost-utility partitioned survival model with a time horizon of 15 years and cycle length of 21 days. The model included three health states: progression-free survival, progressed disease and death. Treatment duration in the model was captured independently from disease progression using time to treatment discontinuation (TTD) survival curves.

For the comparison of talazoparib versus PCT, non-parametric distributions were used in each arm to estimate PFS, OS and TTD for the ITT and subpopulations, using fully mature data from the EMBRACA trial. For the comparison of talazoparib versus carboplatin, unadjusted PFS and OS data from the TNT trial were extrapolated to the full time horizon of the model. Use of unadjusted data in this way does not account for heterogeneity between the EMBRACA and TNT trials and is highly uncertain. Furthermore, as the TNT trial only included patients with TNBC, it was assumed that the efficacy of carboplatin in the entire HER2- population was equivalent to that of a TNBC subpopulation. Considering the poorer prognosis of patients with TNBC, this assumption was considered to underestimate the efficacy of carboplatin. Due to the paucity of clinical evidence available to inform the efficacy of carboplatin and to address the requirement for carboplatin to be included as a comparator, an assumption of equal efficacy between carboplatin and the PCT arm of the EMBRACA trial was also considered by the Review Group. The efficacy of carboplatin in combination with gemcitabine was considered equivalent to that of carboplatin alone. The assumption of equal efficacy between carboplatin in combination with gemcitabine and PCT was therefore also applied. For the comparison of talazoparib versus olaparib, talazoparib

PFS and OS curves were adjusted based on the ITC, to produce the non-parametric PFS and OS curves for olaparib. Olaparib and carboplatin TTD curves were derived from unadjusted OlympiAD and TNT trial data and, as such, failed to account for between-trial heterogeneity.

In the Applicant base case, treatment-specific utility values, based on the EMBRACA trial, were applied in the progression-free survival state. It was assumed that treatment-related AEs were inherently captured by the treatment-specific utility values. A state-specific utility value, based on pooled data from the literature, was applied to the post-progression state. The Review Group considered that health-state specific utility values and separate AE-utility decrements were more appropriate than treatment-specific utilities. This was because of the open-label design of the EMBRACA trial, which can bias patient-reported outcomes in favour of the intervention, and the uncertain clinical relevance of the observed trial results. A one-off cost to account for the cost of a single gBRCAm test was included in all treatment arms of the Applicant base case. This was considered to be inappropriate as gBRCAm testing is not a prerequisite for treatment with current standard of care.

Analyses presented in this summary document are based on the list prices of the intervention and comparators. The NCPE Review Group implemented a number of changes to the Applicant base case to reflect the most plausible assumptions. The most notable of these include: the application of health state-specific utility values to the PFS health state, application of AE-related utility decrements, application of gBRCAm testing costs to the talazoparib and olaparib arms only, assuming the efficacy (PFS and OS) of carboplatin-based regimens were equivalent to that of the PCT arm, assuming the TTD of carboplatin-based regimens and olaparib were equivalent to that of the PCT and talazoparib arms, respectively. Differences were observed between the NCPE-adjusted deterministic and probabilistic ICERs. The probabilistic ICERs are presented as they are considered to be a more accurate reflection of the cost effectiveness of talazoparib, incorporating the results from 1,000 plausible scenarios in which input parameters were varied according to their assigned distribution. The NCPE-adjusted ICERs, based on these assumptions, are presented in Table 1. The probabilistic Applicant base case ICERs are presented in Table 2. All results included below pertain to the ITT population.

Table 1 NCPE-adjusted base case results^

Technologies	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Talazoparib vs PCT	30,238	0.16	184,100
Talazoparib vs Carboplatin monotherapy*	33,599	0.17	198,113
Talazoparib vs Carboplatin-gemcitabine combination	29,052	0.16	185,323
Talazoparib vs Olaparib	-4,506	0.10	Dominant

QALY: quality-adjusted life year; **ICER**: incremental cost-effectiveness ratio; **PCT**: physicians' choice chemotherapy

^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.
*Due to model constraints, the probabilistic sensitivity analysis had to be re-run to obtain probabilistic results for the carboplatin monotherapy arm. As such, the total and incremental QALY figures may not match exactly with the carboplatin-gemcitabine arm despite identical treatment effectiveness assumptions.

Table 2 Applicant base case results^

Technologies	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Talazoparib vs PCT	16,976	0.21	79,295
Talazoparib vs Carboplatin monotherapy*	48,905	0.38	128,004
Talazoparib vs Carboplatin-gemcitabine combination	42,394	0.39	108,901
Talazoparib vs Olaparib	-6,352	0.11	Dominant

QALY: quality-adjusted life year; **ICER**: incremental cost-effectiveness ratio; **PCT**: physicians' choice chemotherapy

^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.
*Due to model constraints, the probabilistic sensitivity analysis had to be re-run to obtain probabilistic results for the carboplatin monotherapy arm. As such, the total and incremental QALY figures may not match exactly with the carboplatin-gemcitabine arm despite identical treatment effectiveness assumptions.

In the NCPE-adjusted base case, talazoparib had a probability of cost effectiveness, versus PCT, of 10.2% at a threshold of €45,000 per QALY, and 5.7% at a threshold of €20,000 per QALY. The probability of cost effectiveness, versus PCT, in the Applicant base case was 35.2% at the €45,000 per QALY threshold and 26.2% at the €20,000 per QALY threshold.

The Review Group conducted an extreme scenario analysis of the NCPE-adjusted base case in order to represent the costs necessary to define the population, including costs for patients who test negative for gBRCAm. In this scenario, all likely testing costs associated with identification of gBRCAm status were incorporated. The probabilistic ICER versus PCT increased to €229,548 per QALY and the probability of cost effectiveness reduced to 1.9% and 4.1% at the €45,000 per QALY and €20,000 per QALY thresholds, respectively.

4. Budget impact of talazoparib

The Applicant applied for reimbursement of talazoparib under the High Tech Drug Arrangement. Talazoparib is available in both 1mg and 0.25mg strength formulations. The price to wholesaler of a 30 tablet pack of talazoparib 1mg tablets is €4,000, while that of a 30 tablet pack of 0.25mg tablets is €1,333.33. When fees and rebate are accounted for, the total cost to the HSE per pack is €4,161.14 and €1,427.80, respectively. Based on the assumption that all patients receive the standard dose of 1mg daily for a duration of 11 months (based on mean TTD from the EMBRACA trial) and a dose intensity of 100%, the total cost of talazoparib is €46,440.04. The dose of talazoparib may be reduced in the event of toxicity, potentially resulting in a reduced cost. When the relative dose intensity from the EMBRACA trial is taken into account, the total cost per treatment course is €42,489.62. This was the cost employed in the budget impact analysis.

Based on the Applicant's assumptions regarding the rate of testing (15-50% HER2-/HR+ population; 90% TNBC population) and the prevalence of gBRCAm in the tested population (5% HER2-/HR+ population; 15% TNBC population), a total of 419 patients are expected to be eligible for treatment with either talazoparib or standard of care over five years. Based on market share, as predicted by the Applicant, a total of 269 patients are expected to be treated with talazoparib, resulting in a cumulative five-year gross drug budget impact of approximately €11.5 million. The five-year net drug budget impact, based on displacement of capecitabine, eribulin, vinorelbine, gemcitabine, and carboplatin in combination with gemcitabine, was estimated to be approximately €10.1 million. When the cost of gBRCAm testing was taken into account, the five-year net budget impact was €13.7 million. The Applicant's net budget impact analysis underestimated comparator costs and may be significantly higher when the actual confidential costs of comparators are taken into account.

The eligible population estimates are heavily dependent on assumptions regarding the rate of gBRCAm testing. Baseline rates of gBRCAm testing are currently very low, but the adoption of widespread testing in response to the availability of a targeted therapy, may significantly increase the eligible population and associated budget impact.

5. Patient submissions

No patient organisation submissions were received during this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that talazoparib (Talzenna®) 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.