NCPE Assessment

Technical Summary

Abemaciclib (Verzenios®)

HTA ID: 22020

19 September 2023

Applicant: Eli Lilly and Company Limited

Abemaciclib in combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of abemaciclib (Verzenios®).

Following assessment of the Applicant's submission, the NCPE recommends that abemaciclib (Verzenios®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Eli Lilly and Company Limited) Health Technology Assessment of abemaciclib (Verzenios®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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 March 2023, Eli Lilly and Company Limited submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of abemaciclib (Verzenios®) in combination with endocrine therapy (abemaciclib + ET) for the the adjuvant treatment of adult patients with hormone receptor positive (HR)-positive, human epidermal growth factor receptor 2 negative (HER2)-negative, node-positive early breast cancer at high risk of recurrence. Eli Lilly and Company Limited is seeking reimbursement of abemaciclib on the High Tech Drug Arrangement.

Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) and is most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth. Abemaciclib is taken orally at a recommended dose of 150mg twice daily. It is taken in combination with endocrine therapy (ET). In pre- or perimenopausal women, aromatase inhibitor ET should be given with a luteinising hormone-releasing hormone (LHRH) agonist. Abemaciclib should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs. Dose interruptions or dose reductions, due to adverse events (AEs), are permitted. The ET is generally taken for at least five years (according to guidelines).

Patients with a high risk of recurrence are typically identified by factors such as number of positive axillary lymph nodes (ALNs), large tumour size and/or tumour grade. Abemaciclib is an add-on therapy to standard of care which is adjuvant ET. ET includes aromatase inhibitors (anastrozole, letrozole and exemestane) or tamoxifen. The comparator for this Health Technology Assessment is ET alone.

1. **Comparative effectiveness of abemaciclib in combination with endocrine therapy**

The monarchE trial is a phase III, global, randomized, open label trial of abemaciclib + ET versus ET alone in patients with HR-positive, HER2-negative, node positive, early stage breast cancer at high risk of recurrence. The monarchE population comprised two cohorts

(Cohort 1 and Cohort 2). The licence relates to Cohort 1 which represents 91% of the overall intention-to-treat (ITT) population.

Cohort 1 comprised participants with either at least four positive ALNs or 1 to 3 positive ALNs and at least one of either histologic grade 3 or tumour size at least 5 cm. Patients were randomised 1:1 to abemaciclib 150mg twice daily in combination with physician's choice of ET (n=2,555) or ET alone (n=2,565). In both arms, patients could receive LHRH agonists as per standard practice. Randomisation was stratified by prior chemotherapy, menopausal status and region. Men were stratified as postmenopausal. Abemaciclib was administered for up to two years or until a discontinuation criterion was met. Dose interruptions or dose reductions, due to AEs, were permitted. In both treatment arms patients received ET to at least study Year 5.

Nearly all participants in Cohort 1 were female (99.4%), and the mean age was approximately 52 years. Approximately 56.6% of participants were post-menopausal, and 84.6% had an Eastern Co-operative Oncology Group score of 0. There were no significant differences in terms of observed characteristics between treatment groups.

At the data cut-off date for a prespecified overall survival (OS) interim analysis (01 July 2022) the median follow-up time for the ITT population was 42 months. In the ITT population, 81.3% of patients in the abemaciclib + ET arm completed the two-year study treatment period (abemaciclib + ET or ET alone). However, only 69% completed two years of abemaciclib + ET; the remaining patients had discontinued abemaciclib early or never received treatment. In the control arm 81.7% completed the two-year treatment period of ET alone. More patients in the abemaciclib + ET group discontinued all study treatment due to AEs compared with the ET alone group (6.4% versus 1.1%). In Cohort 1, abemaciclib + ET was associated with improved invasive disease-free survival (IDFS) (hazard ratio (HR) of 0.65; 95% CI 0.57 to 0.75) and improved distant-relapse free survival (DRFS) (HR of 0.65, 95% CI 0.56 to 0.76), as compared to ET alone. OS data were immature and statistical significance was not reached (HR of 0.89, 95% CI 0.71 to 1.11).

The extent to which the IDFS and DRFS benefit observed to date in the monarchE will translate into a long-term OS benefit remains uncertain. Furthermore, patients remain at risk of recurrence beyond the trial follow-up period**.** Patients with HR-positive early breast cancer have greater risk of late recurrence than those with HR-negative disease. Approximately 50% of recurrences are expected to occur after five years. There is uncertainty as to whether abemaciclib is associated with improved IDFS or with a delay to IDFS events. In addition, investigator bias cannot be excluded owing to the open label nature of the trial and lack of independent assessment of endpoints.

2. Safety of abemaciclib in combination with endocrine therapy

Safety data for abemaciclib + ET for use in early breast cancer is based on data from the monarchE trial. Although the licence relates to Cohort 1, the safety data represents the full safety population (all patients who received at least one dose of study treatment). Also, the safety profile of abemaciclib has previously been evaluated in the metastatic setting. Special warnings and precautions for use associated with abemaciclib include neutropenia, infections, venous thromboembolism, increased aminotransferases, diarrhoea and interstitial lung disease. Concomitant use of CYP3A4 inducers and/or inhibitors should be avoided.

From the most recent monarchE data-cut (1 July 2022), the most common Grade 3 to 4 AEs in the safety population were neutropenia (19·6% of patients in the abemaciclib + ET group versus 0·9% of patients in the ET alone group), leukopenia (11·4% vs 0·4%), and diarrhoea (7·8% vs 0·2%). Serious AEs occurred in 15·5% of patients in the abemaciclib + ET group versus 9·1% of patients in the ET alone group. There were two treatment-related deaths in the abemaciclib + ET group (diarrhoea and pneumonitis) and none in the ET alone group.

3. Cost effectiveness of abemaciclib in combination with endocrine therapy

Methods

A cohort-level state transition model comprising five main health states was used. The model population was based on Cohort 1 of the monarchE trial. A lifetime horizon was adopted. The health states were IDFS, Non-Metastatic Recurrence, Remission, Metastatic Recurrence (MR) and Death. Only patients who die in the IDFS, Non-Metastatic Recurrence

and Remission health states move to the death health state. The MR health state was a separate, absorbing health state with two sub-states. Patients in the IDFS health state, who experienced a disease recurrence while receiving adjuvant ET or within 12 months of completing adjuvant ET, entered the ET-resistant metastatic pathway. Patients who experienced a disease recurrence, more than 12 months after completing their adjuvant ET, entered the ET-sensitive metastatic pathway.

The treatment effects captured by the cost-effectiveness model were the prevention of metastatic and non-metastatic breast cancer recurrence, leading to improved survival and quality of life. The key efficacy inputs in the cost-effectiveness model were IDFS and the proportion of recurrences that were metastatic, both of which were sourced from the monarchE trial. Utilities in the IDFS health state were estimated from the monarchE trial. Utilities for other health states were identified from the literature.

The Review Group had a number of concerns with the Applicant base case. which included the following:

- Parametric extrapolations of the immature IDFS data from monarchE are subject to considerable uncertainty.
- The Gompertz distribution was used to extrapolate IDFS. This predicted a cumulative recurrence risk of 71%, over a lifetime horizon, in the ET alone arm. This is clinically implausible.
- It is assumed that the full treatment benefit for abemaciclib + ET relative to ET alone would be maintained up to Year 8 (i.e. six years following abemaciclib treatment completion). Furthermore, the waning effect occurs very slowly, with some treatment benefit being maintained until Year 27**.**
- Limited information on the methods and data sources used to estimate post-MR costs, life years and quality-adjusted life years (QALYs) was provided. Furthermore, costs and outcomes post-MR are assumed to be the same regardless of the time at which MR occurs; this is not plausible. This assumption could not be changed due to the model structure.
- It was assumed that patients who have received abemaciclib in the adjuvant setting would not be retreated with a CDK4/6 inhibitor in the metastatic setting.

Model functionality allowed the Review Group to address some of the above concerns in the NCPE adjusted base case:

- The log-normal distribution was used to model IDFS. The resultant cumulative recurrence risk of 51%, over a lifetime horizon, in the ET alone arm is in line with clinical opinion and a real-world evidence study.
- Treatment waning begins at end of available trial follow-up (i.e. approximately 4.5 years) and wanes over a period of five years. This reflects the available efficacy data for abemaciclib, clinical opinion, and maintains consistency with previous NCPE assessments in early breast cancer.
- In line with clinical opinion, retreatment with CDK4/6 inhibitors was assumed to occur for some patients in the ET-sensitive metastatic pathway.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively.

Table 1 NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ET alone	52,970	9.90	-	-	-
Abemaciclib + ET	105,280	10.58	52,310	0.68	77,224

ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations =€76,634/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

Table 2 Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ET alone	65,261	9.26	-	-	-
Abemaciclib + ET	102,759	10.17	37,498	0.92	40,869

ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations =€40,328/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

Sensitivity analysis

Under the NCPE adjusted base case the probabilities of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 0% and 1%, respectively. Under the Applicant's assumptions, the probabilities of cost-effectiveness were 0% at the €20,000 per QALY threshold and 70% at the €45,000 per QALY threshold. The duration of treatment effect was not varied in the probabilistic sensitivity analysis; therefore, these probabilities do not reflect the full extent of uncertainty in the cost-effectiveness model.

The Review Group conducted further targeted sensitivity and scenario analyses on IDFS extrapolations and treatment waning assumptions, which are regarded as the key areas of uncertainty in the cost-effectiveness model. Considering the range of plausible scenarios that were explored, it likely that the true ICER lies somewhere in the range of €60,000 to €100,000 per QALY.

4. Budget impact of abemaciclib in combination with endocrine therapy

The price to wholesaler for one pack of abemaciclib film-coated tablets (pack size of 56 tablets containing either 50mg, 100mg or 150mg abemaciclib) is €2,840.73. Assuming a two-year stopping rule for abemaciclib and a five-year stopping rule for ET, the total cost per patient per treatment course is estimated to be €59,701 (including pharmacy fees and applying a Framework Agreement of 8.25%). This cost is based on time-to-treatment discontinuation data and the ET treatment mix from the monarchE trial.

The Applicant predicts 31 patients will receive abemaciclib + ET in Year 1 increasing to 313 patients in Year 5. Applying a two-year stopping rule for abemaciclib and accounting for treatment discontinuations, the Applicant estimated the five-year gross and net drug-budget impacts to be €18.61 million and €18.39 million, respectively.

The Review Group note that packs are flat priced regardless of tablet strength. Therefore, if patients on 150mg twice daily were dispensed both the 50mg and 100mg tablet packs then the cost of abemaciclib per patient would double. Results of the cost-effectiveness analysis and budget impact analysis are made under the assumption that patients on 150mg twice

daily are dispensed the 150mg tablets only.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

6. Conclusion

The NCPE recommends that abemaciclib (Verzenios®) be considered for reimbursement if 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.*