Technology Guidance

Capivasertib

In combination with fulvestrant for HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alteration

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended capivasertib in combination with fulvestrant for inclusion on the MOH List of Subsidised Drugs for HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alteration following disease recurrence or progression on or after an endocrine-based regimen with or without a cyclin-dependant kinase 4/6 inhibitor (CDK4/6i). The decision was based on the uncertain extent of clinical benefit compared with fulvestrant monotherapy, unfavourable cost effectiveness compared with alternative treatments, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for capivasertib are provided in the Annex.

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Technology Evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of capivasertib, in combination with fulvestrant for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (LA/mBC) with one or more *PIK3CA/AKT1/PTEN*-alteration following disease recurrence or progression on or after an endocrine-based regimen with or without a cyclin-dependant kinase 4/6 inhibitor (CDK4/6i). The evaluation considered the company's evidence submission by AstraZeneca for capivasertib (Truqap), and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at public healthcare institutions, the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of capivasertib.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. The Committee heard that each year in Singapore, approximately 460 patients with HR-positive, HER2-negative LA/mBC experience disease recurrence or progression on or after an endocrine-based regimen. Alterations in the AKT pathway (one or more alterations in the *PIK3CA/AKT1/PTEN* genes) occur in approximately 40% of HR-positive, HER2-negative breast cancers and are associated with endocrine resistance and poorer prognosis. Capivasertib is a pan-AKT kinase inhibitor that disrupts signalling in the PIK3/AKT/mTOR pathway, inhibiting cell proliferation, tumour growth and disease progression.

2.2. The Committee noted that following disease progression with an endocrine-based regimen and a CDK4/6i in the metastatic or adjuvant setting, patients are treated mainly with fulvestrant monotherapy, and to a much lesser extent, everolimus plus exemestane, or alpelisib plus fulvestrant (for patients with *PIK3CA* mutations). Locally, capivasertib plus fulvestrant will primarily replace fulvestrant monotherapy.

2.3. The Committee considered the lived experience about advanced breast cancer from one local patient included in the submission and from 14 female patients who provided testimonials to ACE. The Committee heard that breast cancer and treatment side effects such as fatigue, joint pain, and breast pain had negatively impacted their daily activities and ability to work. Patients' mental and emotional well-being was also impacted due to constant fear and anxiety about the future. The Committee noted the financial burden of cancer treatments and its impact on family relationships. The Committee heard that patients with HR-positive, HER2-negative LA/mBC had received different treatments, including docetaxel, letrozole with palbociclib, and capivasertib with fulvestrant. The patient receiving capivasertib reported manageable side effects such as diarrhoea, and changes in taste sensation. The Committee noted that patients valued new treatments with manageable side effects, with some expressing hope for more affordable options that could prolong their survival and improve their quality of life.

Clinical effectiveness and safety

3.1. The Committee noted that the company's requested listing limits the use of capivasertib to the post-CDK4/6i setting. This is a population subset of the HSA-approved indication which does not require prior CDK4/6i use. The Committee considered it more appropriate not to restrict the population to the post-CDK4/6i setting, in line with the overall trial population, as clinicians have identified a small proportion of patients who cannot receive CDK4/6i and may require capivasertib plus fulvestrant.

<u>Capivasertib plus fulvestrant versus fulvestrant monotherapy</u>

3.2. The Committee reviewed the clinical evidence in the company's submission, from a phase III, double-blind, randomised controlled trial (CAPItello-291) that compared capivasertib plus fulvestrant with placebo plus fulvestrant in patients with LA/mBC following disease recurrence or progression on or after an aromatase inhibitor and with or without a CDK4/6i. The evaluation focused on the AKT pathway-altered population, which aligned with the HSA-approved indication.

3.3. In the AKT pathway-altered population, capivasertib plus fulvestrant was associated with a statistically significant improvement in progression-free survival (PFS) compared with placebo plus fulvestrant (median 7.3 versus 3.1 months; hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.38 to 0.65, p<0.001). A similar improvement was seen in the post-CDK4/6i subgroup. While the analyses in the exploratory post-

CDK4/6i subgroup were pre-specified, these analyses were not formally tested for statistical significance.

3.4. The Committee noted that there was no statistically significant difference in overall survival (OS) observed between treatment arms in both the AKT pathway-altered population (HR 0.88, 95% CI 0.65 to 1.19, p=0.408) and post-CDK4/6i subgroup. They considered that capivasertib plus fulvestrant provided a moderate PFS benefit compared to fulvestrant monotherapy, but it was uncertain whether such an improvement could translate to a clinically meaningful gain in long-term OS, given the lack of an established PFS-OS surrogacy relationship.

3.5. For safety outcomes, the Committee noted that capivasertib plus fulvestrant had higher incidence of grade 3 or higher adverse events (AEs; 43.2% versus 16.5%), AEs leading to treatment discontinuation (6.5% versus 0.8%) and serious AEs (18.7% versus 10.5%) compared with placebo plus fulvestrant. They considered the combination therapy to be inferior to fulvestrant monotherapy in terms of safety.

Capivasertib plus fulvestrant versus alpelisib plus fulvestrant and everolimus plus exemestane

3.6. In the absence of direct evidence comparing capivasertib plus fulvestrant with alpelisib plus fulvestrant or everolimus plus exemestane, the Committee reviewed the network meta-analysis (NMA) presented in the submission, which included ten trials for PFS and six trials for OS outcomes.

3.7. The Committee noted that the populations of the included trials were heterogeneous, with inadequate representation of the target AKT pathway-altered population. While the NMA showed numerical improvements in PFS and OS for capivasertib plus fulvestrant compared with alpelisib plus fulvestrant and everolimus plus exemestane, the Committee considered these treatment options to likely offer similar clinical benefits, given the NMA's limitations and that the 95% credible intervals for HRs included 1.

3.8. The Committee noted that as the submission's NMA did not include safety comparisons, no conclusions could be drawn about the relative safety of these treatment options.

Cost effectiveness

Capivasertib plus fulvestrant versus fulvestrant monotherapy

4.1. The Committee considered the results of the submission's cost-utility analysis that compared capivasertib plus fulvestrant with fulvestrant monotherapy for AKT pathway-altered, HR-positive, HER2-negative LA/mBC, based on CAPItello-291 trial data. Key components of the base-case economic evaluation are summarised in

Table 1.

Table 1: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with AKT pathway-altered LA/mBC, with prior CDK4/6i treatment
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	10 years in the model base case, based on a median follow-up of 16.4 months in the CAPItello-291 trial
Health states	Pre-progression; post-progression; death
Cycle length	1 month
Extrapolation methods used to generate results	Extrapolation of the PFS and OS curves were informed by time-to-event data from CAPItello-291 trial and fitted using standard parametric distributions in the base case: • PFS for placebo plus fulvestrant arm = gamma distribution • OS for placebo plus fulvestrant arm = exponential distribution HRs obtained from the NMA was applied to the placebo plus fulvestrant PFS and OS curves to generate the PFS and OS curves for capivasertib plus fulvestrant.
Health-related quality of life	Utilities for progression-free and progressed disease health states were informed by EQ-5D data from the CAPItello-291 trial. • Progression-free health state: 0.780 • Progressed disease health state: 0.722
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LA/mBC, locally advanced or metastatic breast cancer; LY, life year; NMA, network meta-analyses; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year;

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$105,000 and SG$135,000 per quality-adjusted life year (QALY) gained in the post-CDK4/6i subgroup. However, the Committee considered the ICER to be highly uncertain and likely underestimated, in view of the following:

- The application of HR from the NMA to extrapolated curves of the fulvestrant arm to generate OS and PFS curves of capivasertib plus fulvestrant was associated with uncertainty. This is due to inherent issues with the NMA and poor visual fit of the generated curves for the capivasertib plus fulvestrant arm to the observed Kaplan-Meier (KM) curves from the CAPItello-291 trial.

- Cost of treatment with capivasertib plus fulvestrant was likely underestimated. The time-to-treatment-discontinuation (TTD) curve derived by the submission (by applying HR on PFS) was lower than the actual TTD curve observed.

- Reliance on data from the post-CDK4/6i subgroup was considered unnecessarily restrictive, as this subgroup does not represent the full population considered relevant to the local population. The subgroup analysis was exploratory in nature, not formally tested, and the results should therefore be interpreted with caution.

4.3. The Committee considered the revised base case, which accounted for the uncertainties in the company's model. Key changes to the economic model included fitting parametric functions directly to the observed KM curves for the capivasertib plus fulvestrant arm, using actual TTD curve from the trial and using clinical data from the whole AKT pathway-altered population. These changes increased the ICER to between SG$205,000 and $245,000 per QALY gained for the post CDK4/6i subgroup, and more than SG$365,000 per QALY gained for the AKT pathway-altered population.

Capivasertib plus fulvestrant versus alpelisib plus fulvestrant and everolimus plus exemestane

4.4. The Committee noted that a cost-minimisation analysis (CMA) comparing capivasertib plus fulvestrant with alpelisib plus fulvestrant and everolimus plus exemestane was conducted, based on an assumption of similar clinical benefits. The Committee considered the CMA to be secondary to the cost-utility analysis and noted that capivasertib plus fulvestrant was associated with a higher total treatment cost than the comparator regimens.

4.5. Overall, the Committee considered that capivasertib plus fulvestrant did not represent a cost-effective use of healthcare resources for previously treated AKT pathway-altered, HR-positive, HER2-negative LA/mBC at the price proposed by the company.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would increase from between SG$1 million to SG$3 million in the first year, to between SG$3 million and SG$5 million in the fifth year of listing capivasertib on the MOH List of Subsidised Drugs for treating AKT pathway-altered, HR-positive, HER2-negative LA/mBC.

5.2. The Committee considered that the submission estimates were high and uncertain, primarily due to optimistic assumptions on the genetic testing rate and the uncertain uptake rate of capivasertib plus fulvestrant. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million over the first five years of listing. The

Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing capivasertib in combination with fulvestrant on the MOH List of Subsidised Drugs for treating HR-positive, HER2-negative LA/mBC with one or more *PIK3CA/AKT1/PTEN*-alteration following disease recurrence or progression on or after an endocrine-based regimen with or without a CDK4/6i. The decision was based on the uncertain extent of clinical benefit compared with fulvestrant monotherapy, unfavourable cost effectiveness compared with alternative treatments, and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Capivasertib 160 mg and 200 mg film-coated tablets	Capivasertib, in combination with fulvestrant, for the treatment of adult patients with HR-positive, HER2-negative LA/mBC with one or more *PIK3CA/AKT1/PTEN*-alteration following recurrence or progression on or after an endocrine-based regimen with a CDK4/6i.	Not recommended for subsidy	Not recommended for MediShield Life claims