Technology Guidance

Elacestrant

for ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating *ESR1* mutation

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended elacestrant for inclusion on the MOH List of Subsidised Drugs for ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating *ESR1* mutation following disease progression after at least 12 months of endocrine therapy plus cyclin-dependent 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 claims eligibility for elacestrant are provided in the Annex.

Published: 1 July 2026

Technology Evaluation

1.1. At the April 2026 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of elacestrant for the treatment of postmenopausal women, and men, with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (LA/mBC) with an activating oestrogen receptor 1 (*ESR1*) mutation who have disease progression following ≥12 months of endocrine therapy (ET) plus cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). The evaluation considered the company's evidence submission by A. Menarini for elacestrant (Orsedu), and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of elacestrant.

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 155 patients with ER-positive, HER2-negative LA/mBC experience disease progression after initial ET plus CDK4/6i. *ESR1* mutations occur in approximately 48% of these patients and are associated with resistance to ET and poorer prognosis. Elacestrant is an oral selective oestrogen receptor degrader that inhibits ER-directed gene transcription and *ESR1*-mutated tumour growth.

2.2. The Committee noted that following disease progression after ET plus CDK4/6i, patients are mainly treated with fulvestrant monotherapy, and to a much lesser extent, everolimus plus exemestane and alpelisib plus fulvestrant (for patients with *PIK3CA* mutations). Locally, elacestrant will primarily replace fulvestrant monotherapy.

2.3. The Committee considered 24 testimonials from local patients describing their experiences living with breast cancer and the treatments they have received. The Committee heard that breast cancer impacted their emotional and mental health, causing anxiety, depression and uncertainty about their long-term prognosis. The Committee noted that the condition and treatment side effects, such as fatigue and joint pain, affected their daily activities and work performance. The Committee acknowledged that most respondents had financial concerns regarding their treatments and expressed a preference for oral treatments over injectable options. The Committee noted that while patients had not heard of elacestrant, they valued new treatment options for breast cancer that could prevent the cancer from spreading and improve their quality of life.

Clinical effectiveness and safety

3.1. The Committee noted that the company's requested listing restricts elacestrant to patients with an activating *ESR1* mutation and disease progression after ≥12 months of ET plus CDK4/6i. This represents a subset of the broader HSA-approved indication, which does not include the ≥12-month ET duration requirement. Given that clinicians indicated they would use elacestrant in patients with an activating *ESR1* mutation regardless of prior ET duration, the Committee considered it more appropriate to align with the HSA-approved indication.

Elacestrant versus ET

3.2. The Committee reviewed clinical evidence from the company's submission. The phase III, open-label, randomised controlled trial (EMERALD) compared elacestrant with endocrine monotherapy (aromatase inhibitors [AIs] or fulvestrant) in patients with ER-positive, HER2-negative LA/mBC who had disease progression after one or two prior lines of ET, including a CDK4/6i. The Committee noted that the trial was powered to detect differences in efficacy in the intent-to-treat population and overall *ESR1*-mutation subgroup only. However, the evaluation focused on the post-hoc analysis of patients with an activating *ESR1* mutation and disease progression after ≥12 months of prior ET plus CDK4/6i, with results for the overall *ESR1*-mutation subgroup also included.

3.3. In the overall *ESR1*-mutation subgroup, no statistically significant difference in overall survival (OS) between treatment arms was observed at final analysis (hazard ratio [HR] 0.90; 95% CI 0.63 to 1.30; p=0.58). While a statistically significant improvement in progression-free survival (PFS) was demonstrated (HR 0.55; 95% CI 0.39 to 0.77; p=0.0005), the median PFS gain was modest at 1.91 months. The Committee noted that the clinical relevance of this benefit remained uncertain, as AI monotherapy is not representative of second- or third-line treatment in the local setting and would be expected to have limited efficacy in patients with prior AI exposure. This potentially overestimates the treatment effect from elacestrant in the trial.

3.4. Similarly, post-hoc analysis of patients with an activating *ESR1* mutation and disease progression after ≥12 months of prior ET plus CDK4/6i showed no improvement in OS [redacted]. While PFS appeared to favour elacestrant, the magnitude and reliability of benefit remained uncertain as the analysis was not prespecified and is subject to a high risk of bias.

3.5. The Committee considered elacestrant to have an inferior safety profile compared with ET, as it was associated with a higher incidence of treatment-related adverse events (61.7% versus 46.2%), grade 3 or 4 treatment-emergent adverse events (TEAEs; 27.8% versus 21.7%), and TEAEs leading to dose interruption (21.7% versus 6.6%). The most common TEAEs associated with elacestrant were nausea, vomiting and fatigue.

Elacestrant versus alpelisib plus fulvestrant and everolimus plus exemestane

3.6. In the absence of direct evidence, the Committee reviewed unanchored matching-adjusted indirect comparisons (MAICs) presented in the submission. The MAICs used real-world evidence (RWE) to compare the treatment effects of elacestrant with alpelisib plus fulvestrant and of everolimus plus exemestane in the respective subgroups. However, the Committee noted that these analyses were associated with methodological limitations, including post-hoc population selection, risks inherent to RWE, and potential unmeasured confounding, which introduced considerable uncertainty in the results.

3.7. The Committee noted that the submission did not include safety comparisons between elacestrant and these comparators. Overall, the Committee considered that, based on the evidence submitted, the comparative efficacy and safety of elacestrant versus alpelisib plus fulvestrant and everolimus plus exemestane was uncertain.

Cost effectiveness

Elacestrant versus ET

4.1. The Committee considered the results of the submission's cost-utility analysis (CUA) comparing elacestrant with ET in patients with ER-positive, HER2-negative LA/mBC with an activating ESR1 mutation, based on the EMERALD trial. The CUA focused on the post-hoc subgroup of patients with an activating ESR1 mutation and disease progression after ≥12 months of prior ET plus CDK4/6i, with results for the overall ESR1-mutation subgroup also presented. 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	ER+, HER2- LA/mBC with an activating *ESR1* mutation and disease progression after ≥12 months of prior ET + CDK4/6i
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 base-case model versus median duration of follow-up of 27.5 months (elacestrant) and 25.8 months (ET) in the EMERALD trial.
Health states	Progression-free; Progressed disease divided into those receiving chemotherapy and those not receiving chemotherapy; Death
Cycle length	1 month
Extrapolation methods used to generate results	Extrapolation of the PFS, OS, TCD and TTD curves were informed by time-to-event data from the EMERALD trial and fitted using standard parametric distributions in the base case. Adjustments for prior lines of ET were applied due to baseline imbalances for all the fitted curves, although clinical evidence suggested these adjustments do not significantly alter treatment effects. <u>Elacestrant arm</u> • Independent log-normal models were fitted to each of the survival curves (PFS, OS, TCD, and TTD). <u>ET arm</u> • For OS, the submission applied the hazard ratio (HR = 1.67, DCO Sep 2021) to the elacestrant arm. • Independent log-logistic models were fitted to PFS and TTD, while log-normal was fitted to TCD.
Health-related quality of life	Utilities for progression-free and progressed disease health states were informed by EQ-5D data from the EMERALD trial. • Progression-free health state: 0.745 • Progressed disease health state: 0.711
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DCO, data cut-off; ET, endocrine therapy; *ESR1*, oestrogen receptor 1 mutation; ER+, oestrogen receptor positive; EQ-5D, EuroQol 5-Dimension 5-Level; HER2-, human epidermal growth factor receptor 2 negative; ICER, incremental cost-effectiveness ratio; LA/mBC, locally advanced or metastatic breast cancer; LY, life years; PFS, progression-free survival; QALY, quality-adjusted life year; OS, overall survival; TCD, time-to-chemotherapy; TTD, time-to-discontinuation of treatment.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$45,000 and SG$75,000 per quality-adjusted life year (QALY) gained in the post-hoc subgroup of patients with an activating *ESR1*-mutation and ≥12 months of prior ET plus CDK4/6i. However, the Committee considered the ICER to be highly uncertain and likely underestimated given:

- Selection of uncertain and optimistic survival extrapolations, potentially overestimating the incremental benefits of elacestrant over a 10-year time horizon.
- Application of different drug costs and healthcare resource utilisation inputs arising from the use of alternative data sources and assumptions, which favoured elacestrant.
- Assumption of an OS benefit for elacestrant despite no OS improvement observed in the final analysis of the EMERALD trial.

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 applying no OS benefit for elacestrant, and correcting costs and resource utilisation assumptions. These changes increased the ICER to more than SG$365,000 per QALY gained.

Elacestrant versus alpelisib plus fulvestrant and everolimus plus exemestane

4.4. Given uncertainties in the comparative clinical evidence, the Committee compared the treatment costs of elacestrant versus alpelisib plus fulvestrant and everolimus plus exemestane based only on drug and *ESR1*-mutation testing costs. The Committee considered these analyses to be secondary to the CUA, and noted that elacestrant was associated with a higher total treatment cost than the comparator regimens.

4.5. Overall, the Committee considered that, at the price proposed by the company, elacestrant did not represent a cost-effective use of healthcare resources for treating ER-positive, HER2-negative LA/mBC with an activating *ESR1* mutation and disease progression following ≥12 months of ET plus CDK4/6i.

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$3 million and SG$5 million in the first year, to between SG$5 million and SG$10 million in the fifth year of listing elacestrant on the MOH List of Subsidised Drugs for treating ER-positive, HER2-negative LA/mBC with an activating *ESR1* mutation and disease progression after ≥12 months of ET plus CDK4/6i.

5.2. The Committee considered that the submission estimates were high and uncertain. This was due to the complex multi-step approach, which created a risk of double counting, and uncertainty in the uptake rates of both elacestrant and *ESR1*-mutation testing in clinical practice. The Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

5.3. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to increase from less than SG$1 million in the first year, to between SG$1 million and SG$3 million in the fifth year of listing.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing elacestrant on the MOH List of Subsidised Drugs for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative LA/mBC with an activating *ESR1* mutation who have disease progression following ≥12 months of ET plus 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	Eligible for MediShield Life claims
Elacestrant 86 mg and 345 mg film-coated tablets	Elacestrant for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating *ESR1* mutation who have disease progression following ≥12 months of endocrine therapy plus CDK4/6 inhibitor.	Not recommended for subsidy	No

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1; HER2, human epidermal growth factor receptor 2.