NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using elacestrant in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2024

Note that this document is not NICE's final guidance on elacestrant. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using elacestrant in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 October 2024
- Second evaluation committee meeting: 12 November 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Elacestrant is not recommended, within its marketing authorisation, for treating oestrogen receptor (ER)-positive HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 1 line of endocrine therapy including a cyclin-dependent kinase (CDK) 4 and 6 inhibitor in:

- women, trans men and non-binary people after menopause
- men.

1.2 This recommendation is not intended to affect treatment with elacestrant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

ER-positive, HER2-negative is the most common type of breast cancer. After prolonged hormone therapy, the cancer may develop an activating mutation (genetic change) in the oestrogen receptor gene (ESR1). There are no targeted treatments for ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation available on the NHS. For this evaluation, the company asked for elacestrant to be considered for ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation that gets worse only after at least 12 months of treatment with endocrine therapy and a CDK 4 and 6 inhibitor.

For breast cancer that also has a mutation in the PIK3CA gene, standard care is alpelisib plus fulvestrant. Standard care for breast cancer without a PIK3CA mutation is everolimus plus exemestane. For people who cannot have either of these treatment combinations, tamoxifen or chemotherapy may be offered.

There are no clinical trials directly comparing elacestrant with standard care. Indirect comparisons with standard care suggest that elacestrant increases how long people have before their breast cancer gets worse. But these results are uncertain because the company's target population was chosen after the trial data had already been collected and the sample sizes were small. So, the results could be because of chance. There are also limitations in the methods used to do the indirect comparisons.

There are also uncertainties in the economic model, so the cost-effectiveness estimates are uncertain. Even when considering elacestrant's effects on quality and length of life, the most likely cost-effectiveness estimate is above what NICE considers an acceptable use of NHS resources. So, elacestrant is not recommended.

2 Information about elacestrant

Marketing authorisation indication

2.1 Elacestrant (Korserdu, Menarini Stemline) is indicated for the 'treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for elacestrant.

Price

2.3 The company considers the proposed list price for elacestrant (pack of 28 tablets) to be confidential and cannot be reported here until the final draft guidance is published.

2.4 The company has a commercial arrangement, which would have applied if elacestrant had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Menarini Stemline, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Oestrogen receptor-positive HER2-negative advanced breast cancer with an activating ESR1 mutation

3.1 Oestrogen receptor (ER) positive, HER2-negative is the most common subtype of breast cancer. In about 35% of people with early or locally advanced breast cancer, it progresses to metastatic disease within 10 years of diagnosis. And about 13% of people have advanced or metastatic breast cancer at first diagnosis. Up to 50% of breast cancers treated with endocrine therapy such as an aromatase inhibitor develop mutations in the oestrogen receptor gene, ESR1, on disease progression. The clinical experts explained that an ESR1 mutation is more likely to occur the longer the person is having endocrine therapy. They explained that disease progression tends to be faster for breast cancer with an ESR1 mutation and is associated with worse survival than breast cancer without an ESR1 mutation. The committee acknowledged that ER-positive HER2-negative advanced breast cancer with an ESR1 mutation can have poorer outcomes than breast cancer without an ESR1 mutation.

ESR1 mutation testing

3.2 The clinical experts explained that because ESR1 mutations are acquired after endocrine therapy, testing to detect the ESR1 mutation is needed at the point of disease progression after treatment. This can be done using either a repeat tumour biopsy or circulating tumour deoxyribonucleic acid (ctDNA) testing. The Cancer Drugs Fund clinical lead noted the summary of product characteristics for elacestrant states that blood plasma specimens should be used to test for ESR1 mutations, so ctDNA testing would be appropriate. They advised that there is only 1 NHS centre, the

North Thames NHS Genomic Laboratory Hub, that provides ctDNA testing for ESR1 mutation (Marsden360 assay). It would take time to implement ESR1-mutation testing across other centres. The committee acknowledged that ESR1-mutation testing is not routinely done in the NHS and that ctDNA testing on blood plasma specimens would be the proposed approach in line with the summary of product characteristics for elacestrant.

Impact of the condition

3.3 The patient experts explained that living with incurable breast cancer can be distressing for the person and their family and carers, affecting all aspects of their lives. They described the stress of the uncertainty, living in fear and feelings of hopelessness and sadness. These can have a profound impact on a person's psychological and mental wellbeing. The patient experts emphasised the financial impact and explained that carers and children may have to take time off from work or school. They emphasised that there are limited treatment options and that breast cancer with an ESR1 mutation is difficult to treat, with some ESR1 variants more difficult to treat than others. They explained that some people find it difficult starting endocrine therapy knowing they may acquire the activating ESR1-mutation. The committee acknowledged that ER-positive HER2-negative advanced breast cancer with an ESR1 mutation can have a negative impact on the person with the condition, and on their family and carers.

Clinical management

Treatment pathway

3.4 There are no NICE guidelines or technology appraisals guidance on managing advanced breast cancer with an ESR1 mutation. For treating hormone receptor (HR)-positive HER2-negative locally advanced or metastatic breast cancer, NICE's technology appraisals 495, 496 and 563 recommend cyclin-dependent kinase (CDK) 4 and 6 inhibitors (palbociclib,

ribociclib and abemaciclib respectively) in combination with an aromatase inhibitor as an initial endocrine-based therapy in adults. The endocrine therapies used in clinical practice in people with breast cancer who have been through the menopause include non-steroidal aromatase inhibitors (anastrozole and letrozole) or tamoxifen, if aromatase inhibitors are not tolerated or contraindicated. Men may have tamoxifen as a first-line endocrine treatment.

For people who have been through the menopause and whose HR-positive HER2-negative advanced breast cancer has recurred or progressed after a non-steroidal aromatase inhibitor, NICE's technology appraisal guidance 421 recommends everolimus plus exemestane. For HR-positive HER2-negative breast cancer that has PIK3CA (phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha) mutation and has progressed after a CDK 4 and 6 inhibitor plus an aromatase inhibitor, NICE's technology appraisal guidance 816 recommends alpelisib plus fulvestrant.

The clinical experts agreed that the treatment pathway reflects NHS practice. They advised that PIK3CA-mutated breast cancer accounts for about 30 to 40% of breast cancer cases. They explained that everolimus plus exemestane and alpelisib plus fulvestrant have serious side effects and some people may prefer not taking them. They noted that tamoxifen may be offered to people who cannot have either of these 2 treatment combination options because of intolerance to side effects or not being well enough to have them. But the clinical experts differed in their opinions about the proportion of people likely to have tamoxifen. One suggested less than 5% while the other suggested between 5% and 10%. The clinical experts also advised that people who could have tamoxifen would likely not be eligible for elacestrant because of differences in the Eastern Cooperative Oncology Group (ECOG) performance status. The Cancer Drugs Fund clinical lead noted data from the Blueteq database over a 5-year period. This suggests that of 5,500 people starting a CDK 4 and 6

inhibitor for advanced or metastatic breast cancer, 500 had everolimus plus exemestane for progressed disease and 300 had alpelisib plus fulvestrant. The clinical experts explained possible reasons for this large gap in numbers between people starting a CDK 4 and 6 inhibitor and those going on to have second-line therapy. This may be because of:

- most people not yet having progressed disease
- some people having oral chemotherapy (capecitabine)
- clinicians' reluctance to use these combination treatment options because of their toxicity and
- many people being referred on to clinical trials.

The patient experts emphasised the lack of targeted treatments for advanced breast cancer with an ESR1 mutation. They explained that the priority for people is that treatments extend life and quality of life and delay the need for chemotherapy, while being safe with tolerable side effects. The committee acknowledged there are no specifically licensed treatments for advanced breast cancer with an ESR1 mutation available on the NHS, and there is a high unmet need. It noted the differences in opinions about standard care. It concluded that people with the condition and their families would welcome safe and effective treatments for advanced breast cancer with an ESR1 mutation that could delay the need for chemotherapy.

Positioning of elacestrant

3.5 The population in the NICE scope and the marketing authorisation is people who have been through the menopause and men with ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation after at least 1 line of endocrine therapy including a CDK 4 and 6 inhibitor. For this evaluation, the company positioned elacestrant in a narrower population than the marketing authorisation. It positioned elacestrant as a treatment for postmenopausal women, and men, with ER-positive HER2-negative locally advanced or

metastatic breast cancer with an activating ESR1 mutation who have disease progression after at least 12 months of treatment with endocrine therapy and a CDK 4 and 6 inhibitor. The company explained that 3 post-hoc subgroups in elacestrant's pivotal trial (EMERALD, see section 3.6) were explored based on duration of previous treatment with endocrine therapy and a CDK 4 and 6 inhibitor: at least 6, 12 and 18 months. It explained that the 12-month subgroup was selected because it showed the most improved progression-free survival in people having elacestrant (8.6 months) compared with those having standard care (1.9 months; Bardia et al. 2024). The Cancer Drugs Fund clinical lead advised that a cut-off of 12 months may be difficult to implement in the NHS and would mean that people who progressed earlier (for example, after 10 or 11 months) would not be eligible for elacestrant. The clinical experts explained that although 12 months may seem an arbitrary cut off, typically the acquired ESR1 mutation would occur the longer a person has had endocrine therapy. They noted that about 75% to 80% of people would have a CDK 4 and 6 inhibitor for 12 months or more. They explained that in NHS clinical practice, people with ER-positive HER2-negative advanced breast cancer are routinely scanned every 3 to 4 months to check for progression and treatments are usually changed within 2 to 3 weeks of confirmed progression. The clinical experts agreed that a 12-month cut off was clinically appropriate. The company explained that people whose condition progresses early (at 6 months) are likely to be hormone resistant and would be unlikely to benefit from elacestrant. The clinical experts explained that several mechanisms are involved in endocrine resistance, one of which is the acquired ESR1 mutation. They agreed that 6 months of previous endocrine therapy may likely be too short. The committee noted that the target population was based on post-hoc subgroup analyses from EMERALD. It acknowledged that the 12-month threshold for previous treatment with endocrine therapy and a CDK 4 and 6 inhibitor was arbitrary but concluded it has biological plausibility.

Clinical evidence

Key clinical evidence for elacestrant

3.6 The key clinical-effectiveness evidence for elacestrant came from EMERALD. This was a phase 3, open-label, multicentre trial that compared elacestrant with standard care (physician's choice of fulvestrant, anastrozole, letrozole or exemestane). It included 478 postmenopausal women and men 18 years and over, with histologically or cytologically proven ER-positive HER2-negative locally advanced or metastatic breast cancer. The key inclusion criteria were:

- disease progression during or within 28 days after treatment with 1 to 2 previous lines of endocrine therapy for advanced or metastatic breast cancer, including a CDK 4 and 6 inhibitor with fulvestrant or an aromatase inhibitor
- progression during or within 12 months of adjuvant endocrine therapy, considered as 1 line of endocrine therapy for advanced or metastatic cancer
- up to 1 chemotherapy regimen for advanced or metastatic breast cancer
- ECOG performance status 0 or 1 and measurable disease using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or evaluable bone-only disease.

Randomisation was stratified based on ESR1 mutation status, previous treatment with fulvestrant and presence of asymptomatic visceral metastasis. The primary endpoint was progression-free survival assessed by an imaging review committee at a data cut of 2 September 2022. The company clarified that there were no further planned data cuts.

Post-hoc subgroups of elacestrant target population

3.7 Of the EMERALD trial population, 228 had an ESR1 mutation, of which 159 had at least 12 months of previous treatment with endocrine therapy and a CDK 4 and 6 inhibitor. For its target population, the company

presented data for 2 post-hoc subgroups from EMERALD based on different comparators (see section 3.8):

- an activating ESR1-mutation subgroup (n=159; elacestrant compared with everolimus plus exemestane)
- an activating ESR1-mutation and a PIK3CA mutation subgroup; that is, dual mutation (n=62; elacestrant compared with alpelisib plus fulvestrant). This was a subset of the activating ESR1-mutation subgroup.

The committee noted that breast cancer with dual mutation would typically be treated with alpelisib plus fulvestrant (see section 3.4). It noted that the activating ESR1-mutation subgroup included 39% (62/159) of dual mutated breast cancer. It decided that the comparator of everolimus plus exemestane only in the activating ESR1-mutation subgroup did not reflect NHS clinical practice. It decided that the activating ESR1-mutation subgroup comparing elacestrant with everolimus plus exemestane should only include people with breast cancer that had the ESR1 mutation and not the PIK3CA mutation (97/159). It considered that for the company's target population, separate analyses of the 2 distinct subgroups, an activating ESR1-mutation without PIK3CA mutation (n=97) and the dual-mutated subgroup (n=62) should have been done using the appropriate comparators. The committee concluded that the analyses from the company's ESR1-mutation subgroup were not appropriate for decision making because 39% of this subgroup consisted of people that had breast cancer with a dual mutation that had not been compared with alpelisib plus fulvestrant. The committee noted the clinical experts' advice that a very small proportion of people may have tamoxifen, but also noted the large discrepancy in the numbers of people starting a CDK 4 and 6 inhibitor and those progressing onto second-line therapy (see section 3.4). The committee would have liked to have seen scenario analyses that included varying proportions of people having tamoxifen.

Key clinical evidence for the company's selected comparators

3.8 The company used real-world evidence from Flatiron, a database of clinical data from electronic health records completed by cancer care providers in the US, for data on the comparators; everolimus plus exemestane (n=32) and alpelisib plus fulvestrant (n=33). The company selected the Flatiron database because it was the largest breast cancer database that provided relevant comparator efficacy data in people with ER-positive HER2-negative ESR1-positive locally advanced or metastatic breast cancer. The company aligned the inclusion criteria for the Flatiron cohort as much as possible with EMERALD to facilitate matching of patients. Outcomes available from Flatiron were progression-free and overall survival for the whole cohort and also stratified by CDK 4 and 6 inhibitor exposure time.

Indirect treatment comparison

Unanchored matching-adjusted indirect comparisons

3.9 To compare elacestrant with everolimus plus exemestane (in the activating ESR1-mutation subgroup that included the dual-mutated subset) and alpelisib plus fulvestrant (dual mutation only), the company did 2 unanchored matching-adjusted indirect comparisons (MAICs). Unanchored MAICs were done because there were no individual patient-level data (IPD) for the comparators and no common comparator. The company reweighted elacestrant's IPD from EMERALD based on 3 of 14 key patient characteristics to match the mean or median characteristics from the Flatiron subgroups: age, number of previous endocrine therapy lines and previous chemotherapy. Implicitly included characteristics were menopausal status, duration of previous CDK 4 and 6 inhibitor therapy and ESR1 mutation. The company also explained that the EMERALD and Flatiron populations were comprised of women only. The EAG noted that for an unanchored MAIC, there is a strong assumption that all effect modifiers and prognostic factors are accounted for so absolute outcomes can be predicted from covariates. It advised that other key prognostic factors were not included such as tumour grade, circulating tumour cell

count, Ki67 level and family background. The EAG advised that the results from the unanchored MAIC that informed the economic model were highly uncertain because of the limited key prognostic factors that were included in the matching, the small effective sample sizes after weighting, and imbalances in the weighted prognostic factors between arms. The committee acknowledged that the company had done as much as possible to provide comparative evidence for elacestrant with treatments used in the NHS. But it decided that in addition to concerns about the use of post-hoc subgroups from EMERALD (see section 3.7) there are other significant limitations of the unanchored MAICs, leading to high uncertainty in the clinical-effectiveness results that informed the economic model. The committee concluded that it would consider this uncertainty in its decision making.

Clinical effectiveness in the company's target population

EMERALD results

3.10 The EMERALD results showed statistically significantly longer progression-free survival in the elacestrant arm (median 8.6 months) compared with standard care (see section 3.6; median 1.9 months) in the activating ESR1-mutation subgroup that included the dual-mutated subset (hazard ratio 0.41, 95% confidence interval [CI] 0.262 to 0.634; p<0.0001; n=159). Statistically significantly longer progression-free survival in the elacestrant arm (median 5.5 months) compared with standard care (median 1.9 months) was also observed for the dual-mutated subset (hazard ratio 0.423, 95% CI 0.176 to 0.941; n=62). The company provided data on overall survival but these cannot be reported here because the company considers the absolute figures to be confidential. The committee noted that standard care in EMERALD was not representative of NHS clinical practice. It also noted that the subgroups were post-hoc analyses from EMERALD. It concluded that there is uncertainty in the clinical-effectiveness results.

Unanchored MAIC results

3.11 In the activating ESR1-mutation subgroup that included the dual-mutated subset, the company reported improved progression-free and overall survival in the elacestrant arm compared with everolimus plus exemestane. In the dual-mutated subset, the company reported improved progression-free and overall survival in the elacestrant arm compared with alpelisib plus fulvestrant, but to a lesser degree than in the overall ESR1-mutation subgroup. The company considers the absolute figures to be confidential, so they cannot be reported. The EAG advised that inferences of statistical significance should not be made because of limitations of the unanchored MAICs (see section 3.9). The committee decided that the results of the unanchored MAICs were highly uncertain because:

- there were methodological limitations (see section 3.9)
- using everolimus plus exemestane as a comparator for the activating ESR1-mutation subgroup was not appropriate because the subgroup included people with dual mutated breast cancer, who would have had alpelisib plus fulvestrant (see section 3.7)
- the data on overall survival may be uncertain.

The committee concluded that it would consider the uncertainty about the clinical effectiveness of elacestrant in its decision making.

Economic model

Company model

3.12 To compare elacestrant with everolimus plus exemestane in the activating ESR1-mutation subgroup and with alpelisib plus fulvestrant in the dual-mutated subgroup, the company used a partitioned survival model. This had 3 health states (progression free, post-progression and death), a 1-week model cycle with no half-cycle correction and a 37-year time horizon. Everyone enters the model in the progression-free health state and starts treatment. The proportion of people in the health states is determined by survival curves fitted to time to treatment discontinuation,

progression-free survival and overall-survival data from EMERALD for elacestrant, and to Kaplan–Meier curves from the Flatiron dataset for the comparators. During each model cycle, people in the progression-free state can be on-treatment or off-treatment depending on time to treatment discontinuation. The company modelled treatment duration for elacestrant and the comparators differently (see section 3.14). The committee concluded that the company's partitioned survival model structure is appropriate for decision making.

Survival extrapolations

3.13 To extrapolate the long-term effects of elacestrant and the comparators on progression-free and overall survival in the activating ESR1-mutation subgroup and in the dual-mutated subgroup, the company used IPD from EMERALD (elacestrant) and pseudo patient-level data from Kaplan–Meier curves from the Flatiron dataset (everolimus plus exemestane or alpelisib plus fulvestrant). It applied weights from the MAICs to elacestrant IPD to align with prognostic characteristics in the Flatiron comparators. It selected survival distributions based on fit to the Kaplan–Meier estimates using visual inspection, goodness-of-fit statistics and clinical plausibility of long-term extrapolations. Across both subgroups and outcomes, the company and the EAG agreed on all the progression-free and overall survival extrapolations except for the distribution for overall survival for elacestrant in the activating ESR1-mutation subgroup. The company preferred the loglogistic distribution, but the EAG preferred the gamma distribution. The EAG explained that there was no observed overall-survival difference after 3 years. Clinical advice to the EAG was that it is plausible to assume similar overall survival for elacestrant and everolimus plus exemestane after 5 years. The EAG preferred the gamma distribution because beyond 5 years there was a natural convergence of the elacestrant and everolimus plus exemestane survival curves, with the comparator overall-survival curve then becoming slightly higher. It advised that this had little effect on the results. The clinical experts at the committee meeting advised that it would be unlikely for everolimus plus

exemestane to have better overall survival at 5 years than elacestrant. The committee noted that there was crossing in the Kaplan–Meier curves before 3 years and the company confirmed that people had stopped treatment by the time the Kaplan–Meier curves had crossed. The committee noted that there was little difference in the fit across the different curves up to 3 years, but after 3 years the extrapolations are highly uncertain. It decided the EAG's gamma distribution provided the better fit but would have preferred that overall survival was capped such that the treatment effect of everolimus plus exemestane was not higher than elacestrant at and beyond the point of convergence at about 5 years. The committee decided there was high uncertainty in the extrapolations because they were based on data from the unanchored MAICs (see sections 3.9 and 3.11). More importantly, it noted that the extrapolations for the activating ESR1-mutation subgroup are not appropriate for decision making because the subgroup included the dual-mutated subset. It concluded that there was high uncertainty about the extrapolations for the activating ESR1-mutation subgroup.

Modelling treatment duration

3.14 To model treatment duration for elacestrant and the comparators, the company used Kaplan–-Meier data from EMERALD for elacestrant. For the comparator, the company assumed that time to treatment discontinuation was equal to progression-free survival because data on treatment duration were not available from Flatiron. The EAG advised that there was a potential for bias in favour of elacestrant by assuming time to treatment discontinuation for the comparators was equal to progression-free survival. The EAG explained this may overestimate the treatment costs of the comparators relative to elacestrant if people stopped the comparator treatments before progression, as had been observed for elacestrant. To model earlier discontinuation of the comparators, the EAG provided scenario analyses. These adjusted the time to treatment discontinuation curves of the comparators using an assumed hazard ratio (0.8 for the activating ESR1-mutation subgroup and 0.5 for the dual-

mutated subgroup) relative to their progression-free survival. The EAG explained that these hazard ratios were selected to provide a similar time to treatment discontinuation in the comparator arms as for elacestrant. One clinical expert suggested that for the dual-mutated subgroup, about 40% of people stop alpelisib plus fulvestrant before disease progression because of toxicity. The committee noted the clinical experts' advice that many people stop treatment with everolimus plus exemestane and alpelisib plus fulvestrant because of toxicity (see section 3.4). So, the committee decided it was inappropriate to assume that time to treatment discontinuation for the comparators is equal to progression-free survival. It would have preferred to have seen analyses based on evidence of treatment discontinuation for the comparators. It also noted that the analyses with everolimus plus exemestane for the activating ESR1-mutation subgroup are inappropriate because the subgroup included the dual-mutated subset.

Costs

Modelling ESR1 mutation testing

3.15 To model ESR1 mutation testing, the company assumed it costs £300 for each digital polymerase chain reaction test using a blood plasma specimen (based on NIHR's interactive costing tool) and a 50% prevalence of ESR1 mutation (see section 3.1). This gives a cost of £600 for each case identified for treatment. The NHS Genomic Medicine Service (GMS) had provided NICE with cost estimates of ctDNA tests for ESR1 mutation at a current value and a future assumed value using a large next generation sequencing panel in its testing approach. The figures are considered confidential and so cannot be reported here. The Cancer Drugs Fund clinical lead explained that the NHS GMS has advised that for this evaluation the cost of ESR1-mutation testing should be included at the future assumed value with a 50% prevalence rate for a positive test applied to the cost. The committee concluded that the future assumed cost of ESR1-mutation testing (with a 50% prevalence rate for a

positive test) provided by the NHS GMS should be implemented in the base-case analyses for the 2 subgroups.

Severity

Severity of the condition

3.16 The committee considered the severity of the condition (including the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company considers the QALY shortfall estimates to be confidential, so they cannot be reported. Using the company's and EAG's utilities, the QALY shortfall met the threshold for a severity weight of 1.2 in only the activating ESR1-mutation subgroup. But the committee noted that these calculations are inappropriate because the subgroup included the dual-mutated subgroup data. It decided that the absolute and proportional shortfalls generated by the company and the EAG could not be used to inform its decision making on severity for the activating ESR1-mutation subgroup. So, it was unable to conclude if a severity modifier should be applied for the activating ESR1-mutation subgroup. The committee noted that using the company's and EAG's utilities, the QALY shortfall did not meet the threshold for a severity weighting greater than 1 in the dual-mutated subgroup.

Cost-effectiveness estimates

3.17 NICE's health technology evaluations manual notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about

recommending a technology if it is less certain about the ICERs presented.

The committee noted that for the activating ESR1-mutation subgroup none of the company's or EAG's ICERs were relevant, including those from the base case and scenario analyses. This was because the activating ESR1-mutation subgroup included 39% dual-mutated breast cancer cases for which the comparator, everolimus plus exemestane, was not appropriate. So, the related survival extrapolations (see section 3.13) and the severity modifier calculations (see section 3.16) were not appropriate.

For both the activating ESR1-mutation subgroup and the dual-mutated subgroup, the committee decided there was a high level of uncertainty particularly about the:

- composition of the comparator arms, specifically whether tamoxifen and chemotherapy (oral capecitabine) should be included (see section 3.4 and 3.7)
- relative clinical effectiveness of elacestrant, specifically because of the post-hoc nature of subgroups from EMERALD (see sections 3.10 and 3.11) and the methodological limitations of the unanchored MAICs (see section 3.9)
- modelling of treatment duration for the comparators not based on evidence (see section 3.14).

So, the committee concluded that it did not have a preferred ICER for the dual-mutated subgroup. This was mostly because of uncertainty about the relative clinical effectiveness of elacestrant (see section 3.9) and modelling of treatment duration of alpelisib plus fulvestrant (see section 3.14). But the committee noted that for the dual-mutated subgroup, all the ICERs including the company's and EAG's base case and all the scenarios, were above what NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The exact figures

cannot be reported as they are considered confidential because of comparator price discounts.

Areas needing clarification and further analyses

3.18 The committee decided there were many areas of uncertainty (see section 3.17). It would like clarification and further analyses on the:

- company's target population and appropriate modelling of comparators (see section 3.7)
- appropriate extrapolations for progression-free and overall survival, and time to treatment discontinuation, given the target populations and associated comparators (see section 3.13), including:
  - modelling of treatment discontinuation for comparators based on evidence (see section 3.14)
  - cost of ESR1-mutation testing suggested by the Cancer Drugs Fund clinical lead (see section 3.15)
  - calculation of the severity modifier given the target populations and comparators (see section 3.16)
- uncertainty about the relative clinical effectiveness of elacestrant (see sections 3.10 and 3.11). The committee decided that given the high uncertainty about the post-hoc subgroups from EMERALD and the clinical effectiveness of elacestrant relative to the comparators, it would like to see exploratory cost-minimisation analyses that assume equivalent clinical effectiveness on all outcomes such as progression-free and overall survival, time to treatment discontinuation and adverse events.

Other factors

Equality issues

3.19 Stakeholders did not identify any equality issues. The committee noted that although the marketing authorisation for elacestrant is for the 'treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast

cancer with an activating ESR1 mutation', a person can have breast cancer after menopause and not identify as a woman. Gender reassignment is a protected characteristic under the Equality Act 2010. The recommendations in this guidance include women, trans men and non-binary people registered female at birth who have been through the menopause, and men (see sections 1.1 and 3.21).

Innovation

3.20 The committee considered if elacestrant is innovative. The clinical experts advised that elacestrant is a step-change in managing ER-positive HER2-negative advanced or metastatic breast cancer with an activating ESR1 mutation for which there are no targeted treatment options, so there is a high unmet need. They advised that elacestrant's ease of administration in the form of an oral tablet benefits people with breast cancer and the NHS by requiring less time in hospital. The committee did not identify additional benefits of elacestrant not captured in the economic modelling. So, it concluded that all additional benefits of elacestrant had already been taken into account.

Conclusion

Recommendation

3.21 All the ICERs in the company's and EAG's analyses were higher than the range considered to be a cost-effective use of NHS resources. So, elacestrant could not be recommended for routine commissioning in the NHS for treating ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 1 line of endocrine therapy and a CDK 4 and 6 inhibitor in women, trans men and non-binary people after menopause and men.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the elacestrant being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd
Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Sharlene Ting
Technical lead

Nigel Gumbleton

Technical adviser

Jeremy Powell
Project manager

ISBN: [to be added at publication]

Issue date: September 2024