NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations 4

2 Information about elacestrant 6

Marketing authorisation indication 6

Dosage in the marketing authorisation 6

Price 6

3 Committee discussion 7

The condition 7

Clinical management 8

Clinical evidence 12

Indirect treatment comparison 15

Clinical effectiveness in the company's target population 16

Economic model 17

Costs 20

Severity 21

Cost-effectiveness estimates 22

Other factors 23

Conclusion 24

4 Implementation 25

5 Evaluation committee members and NICE project team 26

Evaluation committee members 26

Chair 26

NICE project team 26

1 Recommendations

1.1 Elacestrant is recommended as an option 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 treatment plus a cyclin-dependent kinase (CDK) 4 and 6 inhibitor in:

- women, trans men and non-binary people who have been through the menopause
- trans women and men.

Elacestrant is recommended only if:

- the cancer has progressed after at least 12 months of endocrine treatment plus a CDK 4 and 6 inhibitor, and
- the company provides it according to the commercial arrangement.

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 endocrine treatment, the cancer may develop an activating mutation (genetic change) in the oestrogen receptor gene (ESR1).

For this evaluation, the company asked for elacestrant to only be considered for ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed (got worse) after at least 12 months of endocrine treatment plus a CDK 4 and 6 inhibitor. This does not include everyone it is licensed for.

There are no targeted treatments for ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation. Standard care is usually

everolimus plus exemestane, or for ER-positive HER2-negative PIK3CA-mutated locally advanced or metastatic breast cancer, alpelisib plus fulvestrant.

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.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimate is within the range that NICE considers an acceptable use of NHS resources. So, elacestrant is 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 list price for elacestrant is £7,340 per 28 pack of 345-mg tablets and £2,447 per 28 pack of 86-mg tablets (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes elacestrant available to the NHS with a discount. The size of the discount is commercial in confidence.

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

ER-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. 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 ER 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. They also explained that progression-free survival tends to be lower for breast cancer with mutations in both the ESR1 and PIK3CA genes than for breast cancer with a single gene 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 for an 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 NHS

England Cancer Drugs Fund (CDF) clinical lead noted the summary of product characteristics for elacestrant states that blood plasma specimens should be used for ESR1-mutation testing, so ctDNA testing would be appropriate. The CDF clinical lead advised that currently there are no NHS Genomic Laboratory Hubs performing routine ctDNA testing for ESR1 mutation and such testing would have to be rolled out across the Genomic Medicine Service (GMS) were elacestrant to be recommended by NICE. They advised it would take time to implement ESR1-mutation testing. 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 starting endocrine therapy difficult 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 is no NICE guidance on managing advanced breast cancer with an ESR1 mutation. For hormone receptor (HR)-positive HER2-negative locally advanced or

metastatic breast cancer, NICE's technology appraisals guidance on palbociclib, ribociclib and abemaciclib recommend these cyclin-dependent kinase (CDK) 4 and 6 inhibitors plus an aromatase inhibitor as an initial endocrine-based therapy in adults. Endocrine therapies used in clinical practice for breast cancer in people who have been through the menopause include non-steroidal aromatase inhibitors (anastrozole and letrozole), or tamoxifen if aromatase inhibitors are not tolerated or contraindicated. Trans women and men may have tamoxifen as a first-line endocrine therapy.

For HR-positive HER2-negative advanced breast cancer that has recurred or progressed after a non-steroidal aromatase inhibitor in people who have been through the menopause, NICE technology appraisal guidance recommends everolimus plus exemestane. For HR-positive HER2-negative breast cancer that has a PIK3CA mutation and has progressed after a CDK 4 and 6 inhibitor plus an aromatase inhibitor, NICE technology appraisal guidance 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 combinations 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 their Eastern Cooperative Oncology Group (ECOG) performance status. The CDF clinical lead noted data from the Blueteq database over a 5-year period. It is estimated that, annually, 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 treatment. This may be because of:

- most people not yet having progressed disease

- some people having oral chemotherapy (capecitabine)
- healthcare professionals' reluctance to use the combination treatment options because of their toxicity, and
- many people being referred on to clinical trials.

At the second committee meeting, the clinical experts explained that for breast cancer with a PIK3CA mutation, alpelisib plus fulvestrant is preferred to everolimus plus exemestane. But they noted alpelisib plus fulvestrant can be difficult to tolerate leading to even higher levels of discontinuation in NHS clinical practice than the 30% seen in trials. Some people with a PIK3CA mutation may be offered everolimus plus exemestane because they have diabetes, have had fulvestrant before or their PIK3CA mutation status is not known at the time of progression on a CDK 4 and 6 inhibitor. One clinical expert also explained that response rates to everolimus plus exemestane and alpelisib plus fulvestrant have been lower in NHS clinical practice than seen in the trials. The CDF clinical lead explained that the uptake of alpelisib plus fulvestrant had been low but slowly increased and is now plateauing. The patient experts highlighted there is a high variability in treatment response depending on the ESR1-mutation variant. They explained that the priority for people is that treatments extend life, support 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 and that treatment response may be variable depending on ESR1-mutation variant. 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 plus a CDK 4 and 6 inhibitor. For this evaluation, the company positioned elacestrant for a narrower population than the marketing authorisation. It positioned elacestrant for ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 12 months of endocrine therapy plus 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 plus 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 CDF clinical lead advised that a 12-month cut-off may be difficult to implement in the NHS and would mean that people whose cancer progresses 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 is more likely 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 have routine scans 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 at 6 months are likely to be endocrine 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 plus 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 physician's choice of fulvestrant, anastrozole, letrozole or exemestane. It included 478 women who had been through the menopause 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 independent 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 people had an ESR1 mutation, of which 159 people had at least 12 months of previous treatment with endocrine therapy plus a CDK 4 and 6 inhibitor. For its target population (see section 3.5), the company presented data for 2 post-hoc subgroups from EMERALD:

- Activating ESR1-mutation subgroup (n=159; 78 in the elacestrant arm and 81 in the active control arm). The elacestrant arm was indirectly compared with everolimus plus exemestane.
- Dual-mutated activating ESR1-mutation and PIK3CA-mutation subgroup (n=62; 27 in the elacestrant arm and 35 in the active control arm). The elacestrant arm was indirectly compared with alpelisib plus fulvestrant. This was a subset of the activating ESR1-mutation subgroup.

  The committee noted that dual-mutated breast cancer would typically be treated with alpelisib plus fulvestrant (see section 3.4). It noted that 35% of people included in the elacestrant arm of the activating ESR1-mutation subgroup (27/78) had 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 whose breast cancer had the ESR1 mutation and not the PIK3CA mutation (51/78). It noted that for the company's target population, separate analyses of the 2 distinct subgroups, the activating ESR1-mutation without PIK3CA mutation subgroup (n=51) and the dual-mutated subset (n=27), 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. This was because 35% of this subgroup included people with dual-mutated breast cancer and elacestrant had not been compared with alpelisib plus fulvestrant for these people. The committee noted the clinical experts' advice that a very small proportion of people may have tamoxifen. But, it also noted the large discrepancy in the numbers of people starting a CDK 4 and 6 inhibitor and those progressing onto second-line treatment (see section 3.4). The committee would have liked to have seen scenario analyses that included varying proportions of people having tamoxifen.

  At the second committee meeting, the clinical experts explained that tamoxifen would be used by people who were not well enough to tolerate other treatments. They explained that the aim is to maximise endocrine therapy and delay chemotherapy. The committee concluded that tamoxifen

and chemotherapy are not relevant comparators in this evaluation. In response to the draft guidance consultation, the company maintained its position that although the activating ESR1-mutation subgroup included dual-mutated breast cancer, this subgroup was appropriately compared with everolimus plus exemestane only. The company explained that it had consulted 14 UK clinical experts who agreed that this comparison reflected clinical practice. This is because everolimus plus exemestane would be used regardless of a specific mutation, and when alpelisib plus fulvestrant is contraindicated or not suitable. The company considered that Flatiron, a US-based database of clinical data from electronic health records completed by cancer care providers, was representative of everolimus plus exemestane's use in clinical practice (see section 3.8). It further highlighted that the proportions of dual-mutated breast cancer in EMERALD (35%) and Flatiron (34%) were similar. So, the company did not provide the requested analyses comparing elacestrant and everolimus plus exemestane in a single ESR1-mutation subgroup. The company further explained that this decision was based on the additional time needed to obtain new Flatiron data (about 6 months) and whether the new analyses would address the uncertainties because of the small sample size. The committee noted that the company had already reduced the ESR1-mutation subgroup sample size by about 30% by introducing the 12-month threshold for previous endocrine therapy. It noted that a single ESR1-mutation subgroup would further reduce the sample size. But, it had concerns about whether the activating ESR1-mutation subgroup that included the dual-mutated subset was representative of NHS clinical practice. Specifically, the proportion of those with dual-mutated breast cancer that would have everolimus plus exemestane rather than alpelisib plus fulvestrant. The committee acknowledged the similar proportions of dual mutations in EMERALD and Flatiron but noted that there may be differences in clinical practice in the US and UK. The company explained that the treatment pathway in the US is similar to the UK and reflects international guidelines on everolimus plus exemestane and alpelisib plus fulvestrant. The clinical experts were not able to advise on the generalisability of the activating ESR1-mutation subgroup to NHS clinical practice. The committee acknowledged the company's difficulties in providing the requested analyses for a single ESR1-mutation subgroup. It concluded that it would take into account the uncertainty of everolimus plus exemestane's suitability for some people with dual-mutated breast cancer in

the activating ESR1-mutation subgroup in its decision making.

Key clinical evidence for the company's selected comparators

3.8 The company used real-world evidence from Flatiron, for data on everolimus plus exemestane (n=32) and alpelisib plus fulvestrant (n=33). The company selected Flatiron 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

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 (in the dual-mutatied subset only), the company did 2 unanchored matching-adjusted indirect comparisons (MAICs). Unanchored MAICs were done because there was 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 comprised 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. This was 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 substantial 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 the physician's choice arm (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 the physician's choice arm (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 this cannot be reported here because the company considers the absolute figures to be confidential. The committee noted that the treatments in the physician's choice arm in EMERALD were 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 here. 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 unanchored MAIC results 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 some 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 subset, 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 Flatiron 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 subset, the company used IPD from EMERALD (elacestrant) and pseudo patient-level data from Kaplan–Meier curves from Flatiron (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 log-logistic 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 after 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 the Kaplan–Meier curves crossed before 3 years and the company confirmed that people had stopped treatment by the time the curves had crossed. The committee noted that there was little difference in the fit across the different curves up to 3 years, but after this 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

so that the treatment effect of everolimus plus exemestane was not higher than elacestrant at and beyond the point of convergence at about 5 years.
In response to the draft guidance consultation, the company revised its base case to reflect the committee's preferred assumption for extrapolating overall survival for elacestrant in the activating ESR1-mutation subgroup. It used the gamma distribution to extrapolate overall survival, with the underlying hazard of death capped by the underlying hazard of the everolimus plus exemestane gamma overall survival extrapolation. The committee agreed with the company's revised approach. However, it decided that there was high uncertainty in the extrapolations because they were based on data from the unanchored MAICs (see section 3.9 and section 3.11). It also noted that the extrapolations for the activating ESR1-mutation subgroup may be uncertain because the subgroup included the dual-mutated subset. It concluded that it would consider these uncertainties in its decision making.

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 was 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 subset) 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 subset, 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 were uncertain because the subgroup included the dual-mutated subset. In response to the draft guidance consultation, the company explained that it was unable to identify relevant published evidence on treatment discontinuation for the comparators. The company revised its base case using the EAG's scenario analyses. The committee concluded that the company's updated approach to modelling treatment duration was appropriate for decision making.

Costs

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 the National Institute for Health and Care Research's interactive costing tool). It also assumed a 50% prevalence of ESR1 mutation (see section 3.1). This gives a cost of £600 for each case identified for treatment. The NHS GMS 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 (NGS) panel in its testing approach. The figures are considered confidential and so cannot be reported here. The CDF 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 positive tests applied to the cost. In response to the draft guidance consultation, the company excluded the cost of ESR1-mutation testing in its revised base case. It also disagreed that the cost should be for a larger NGS panel which is higher than the £300 cost for a single ESR1-mutation test. The CDF clinical lead explained that the NHS GMS had taken into account that the ESR1 mutation would be tested alongside other gene mutations on a larger NGS panel and so considered an assumed reduced future cost rather than the higher current cost to be appropriate. The clinical experts explained that, in line with the company's positioning of elacestrant, people whose breast cancer has progressed after at least 12 months of endocrine therapy plus a CDK 4 and 6 inhibitor would be offered an

ESR1-mutation test. But, retesting would not happen after negative tests because people would have moved onto other treatments. The committee concluded that the cost of ESR1-mutation testing should be included in line with NICE's health technology evaluations manual. It agreed that a future assumed value for each case identified (using the cost of the test and a 50% prevalence rate for positive tests) should be implemented in the base-case analyses for the 2 subgroups. It noted that the EAG's revised base case included its preferred assumptions on ESR1-mutation testing. The committee also acknowledged that there would likely be some uncaptured benefits of testing for other mutations on a larger NGS panel and concluded it would take this into account in its decision making.

Severity

3.16 The committee considered the severity of the condition (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 here. In response to the draft guidance consultation, the company revised the mean ages used in its calculations to align with those used in the EAG's calculations. 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 may be uncertain because the subgroup included the dual-mutated subset. It decided that there was uncertainty in the absolute and proportional QALY shortfalls generated by the company and the EAG. It agreed that these uncertainties would be considered in its decision making on severity for the activating ESR1-mutation subgroup. The committee concluded that a severity weighting of 1.2 should be applied to 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 subset.

Cost-effectiveness estimates

Committee's preferred assumptions

3.17 In response to the draft guidance consultation, both the company's and EAG's revised base cases were aligned except for the assumptions about ESR1-mutation testing (see section 3.15). The committee's preferred assumptions were in line with the EAG's revised base case.

Acceptable ICER

3.18 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. But it will also take into account other aspects including uncaptured health benefits. The committee recalled the statements from the clinical and patient experts about the significant unmet need for effective and safe treatments for this condition. It acknowledged that elacestrant is the first targeted treatment for breast cancer with an activating ESR1 mutation. It noted that, as an oral treatment, elacestrant would be easily administered and fit into the existing care pathway. The committee acknowledged the potential uncaptured benefits of ESR1-mutation testing on a larger NGS panel. But, it noted the high level of uncertainty, specifically:

- For the activating ESR1-mutation subgroup, there were uncertainties in the company's and EAG's ICERs. This was because the activating ESR1-mutation subgroup included 35% dual-mutated breast cancer for which the comparator, everolimus plus exemestane, may not be offered. So, the related survival extrapolations (see section 3.13) and the severity modifier calculations (see section 3.16) are uncertain.
- For both the activating ESR1-mutation subgroup and the dual-mutated subset, there were uncertainties in the:

- 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 that was not based on evidence (see section 3.14).

So, considering the uncertainties and uncaptured benefits, the committee concluded that an acceptable ICER for both subgroups would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.19 The committee considered the cost effectiveness of elacestrant in the activating ESR1-mutation subgroup compared with everolimus plus exemestane and in the dual-mutated subset compared with alpelisib plus fulvestrant. In both the company's and EAG's revised base cases, the deterministic and probabilistic ICERs were within the range the committee considered to be acceptable for this evaluation (see section 3.18). The exact cost-effectiveness estimates cannot be reported because of confidential price discounts.

Other factors

Equality issues

3.20 Stakeholders did not identify any equality issues. The committee noted that although the marketing authorisation for elacestrant is for 'postmenopausal women, and men' with the condition, 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, trans women and men

(see section 1.1 and section 3.22).

Uncaptured benefits

3.21 The committee considered if elacestrant is innovative. The clinical experts advised that elacestrant is a step-change in managing ER-positive HER2-negative locally 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 acknowledged the potential uncaptured benefits of ESR1-mutation testing on a larger NGS panel (see section 3.15 and section 3.18).

Conclusion

Recommendation

3.22 All the ICERs in the company's and EAG's analyses were within the range considered to be a cost-effective use of NHS resources. So, elacestrant could be recommended as an option for treating ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation in women, trans men and non-binary people who have been through the menopause, trans women and men. It is only recommended if the cancer has progressed after at least 12 months of endocrine therapy plus a CDK 4 and 6 inhibitor.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has ER-positive HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 12 months of endocrine therapy including a cyclin-dependent kinase (CDK) 4 and 6 inhibitor and the healthcare professional responsible for their care thinks that elacestrant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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, a project manager and an associate director.

Sharlene Ting
Technical lead

Nigel Gumbleton
Technical adviser

Jeremy Powell

Project manager

Emily Crowe
Associate director

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