National Institute for Health and Care Excellence

Health Technology Evaluation

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Menarini Stemline	Menarini Stemline believe this is an important topic for NICE to consider given the lack of targeted therapies for patients who are ESR1 mutation positive, and who consequently have poor prognosis and survival outcomes.[1–4] We believe that Single Technology Appraisal (STA) is the appropriate route. **References** 1. Herzog SK, Fuqua SAW. ESR1 mutations and therapeutic resistance in metastatic breast cancer: progress and remaining challenges. Br J Cancer. 2022;126(2):174–186. https://doi.org/10.1038/s41416-021-01564-x. 2. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021;23(1):85. https://doi.org/10.1186/s13058-021-01462-3.	Comments noted. No action needed.

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		3. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer. JAMA Oncol. 2016;2(10):1310–1315. https://doi.org/10.1001/jamaoncol.2016.1279. 4. Turner NC, Swift C, Kilburn L, et al. ESR1 Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. Clin Cancer Res. 2020;26(19):5172–5177. https://doi.org/10.1158/1078-0432.CCR-20-0224.	
	METUPUK	This is an important evaluation which provides another option for patients who have progressed on CKK [sic] 4/6 inhibitors.	Comment noted. No action needed.
	Breast Cancer Now	Yes this is an appropriate topic and route.	Comment noted. No action needed.
Wording	Menarini Stemline	Menarini Stemline propose the wording of the remit is aligned to the anticipated regulatory wording: "To appraise the clinical and cost effectiveness of elacestrant within its marketing authorisation for treating people with locally advanced or metastatic hormone receptor-positive, HER2-negative, ESR1-mutated breast cancer that has progressed after prior endocrine therapy including a CDK 4/6 inhibitor".	Comment noted. The remit in the scope has been amended to align with the marketing authorisation of elacestrant.
	METUPUK	No comments	No action needed.
	Breast Cancer Now	*(Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.)* Yes	Comment noted. The remit in the scope has been amended to align with the marketing

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			authorisation of elacestrant.
Timing Issues	Menarini Stemline	Menarini Stemline considers the NICE STA route is appropriate to deliver timely guidance to the NHS for this topic. Elacestrant is expected to gain UK marketing authorisation in 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 at least one line of endocrine therapy including a CDK 4/6 inhibitor. ESR1 mutation is an adverse prognostic biomarker in ER-positive breast cancer. The urgency for this appraisal therefore arises from the lack of reimbursed treatment options for patients with hormone receptor-positive, HER2-negative, ESR1-mutated advanced breast cancer.[1, 2, 5] Since ESR1 mutations arise almost exclusively after endocrine therapy in the advanced setting and given that NICE recommends that patients receive an aromatase inhibitor in combination with a CDK4/6 inhibitor as their first treatment in this setting, such patients would be eligible for treatment with elacestrant from this point in the treatment pathway once an ESR1 mutation is confirmed. Therefore, Menarini Stemline believe a timely appraisal should occur to provide the NHS with guidance, given the current unmet need for a targeted therapy for ESR1-mutated patients in this setting. **References** 1. Herzog SK, Fuqua SAW. ESR1 mutations and therapeutic resistance in metastatic breast cancer: progress and remaining challenges. Br J Cancer. 2022;126(2):174–186. https://doi.org/10.1038/s41416-021-01564-x. 2. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast	Comments noted. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta11263

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		cancer. Breast Cancer Res. 2021;23(1):85. https://doi.org/10.1186/s13058-021-01462-3. 5. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med. 2015;7(313):313ra182. https://doi.org/10.1126/scitranslmed.aac7551.	
	METUPUK	There is an unmet need for lines of endocrine directed therapy for patients with hormone receptor-positive HER2-negative MBC. Patients prefer targeted treatments over cytotoxic chemotherapy.	Comments noted. No action needed.
	Breast Cancer Now	Whilst we have seen the welcome introduction of new treatments for hormone receptor-positive, HER2 negative secondary (metastatic) breast cancer, we know that the cancer will eventually become resistant to endocrine therapies so new effective treatments are still desperately needed. The scope mentions a possible subgroup for ESR1. NHS England's Genomic Education Programme estimates that ESR1 mutations are present in up to 20% of secondary ER-positive breast cancers, although estimates vary. As ESR1 can be associated with resistance to endocrine therapies, it is important that new treatments which could potentially benefit this group of patients are assessed for use on the NHS as quickly as possible.	Comments noted. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta11263
Additional comments on the draft remit	Menarini Stemline	None	No action needed.
	METUPUK	No further comments	No action needed.
	Breast Cancer Now	None	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Menarini Stemline	Menarini Stemline suggest adapting the background on breast cancer to ensure it reflects the advanced disease setting (Stage III and IV). An example is the description include in the scope for TA816 (alpelisib plus fulvestrant). Of note is the fact that the eligible patient population for elacestrant is locally advanced and metastatic disease, not only metastatic disease as is currently described in the disease background: Breast cancer arises from the tissues of the ducts or lobules of the breast. The cancer is said to be 'advanced' if it has grown directly into surrounding structures such as the chest wall and cannot be completely removed by surgery or if it has spread to other parts of the body such as the bones, liver, and lungs (metastatic cancer). In 2020 in England, 40,192 people were diagnosed with breast cancer.[6] In 2021 there were 9,120 deaths from breast cancer in England.[7] Approximately 17% of women with breast cancer have advanced disease (stage III or IV) in England when they are diagnosed.[8] The 1-year survival rate for adults diagnosed at stage IV (metastatic breast cancer) in England is 67%.[9] Around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.[10] Menarini Stemline also suggest adding the percentage of people with advanced ER-positive breast cancer with the ESR1 mutation, given the proposed licensed indication is specific to this population: ESR1 mutations are most frequently seen in people who have received aromatase inhibitor (AI) therapy; approximately 20–40% of patients who have	Comments noted. The background section has been updated to include information on locally advanced and metastatic disease and information on ESR1 mutations. The scope background provides a broad outline of the disease area and treatment pathway.

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		received an AI for metastatic breast cancer have ESR1 mutations, with prevalence varying by sites of metastatic disease.[11–17] Menarini Stemline suggest adapting the treatment pathway section to reflect changes in routine clinical practice since the publication of CG81. Suggested text is proposed below: 'NICE clinical guideline 81 (CG81)[18] recommends first-line treatment with endocrine therapy for most people with advanced hormone receptor-positive breast cancer. More recent NICE technology appraisals (495, 496 and 563) have recommended CDK 4/6 inhibitors (palbociclib, ribociclib and abemaciclib respectively) in combination with an aromatase inhibitor as first-line endocrine therapy for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.[19–21] Some patients may still receive endocrine monotherapy first-line. Options include; aromatase inhibitors (anastrozole and letrozole) or tamoxifen, if aromatase inhibitors are not tolerated or are contraindicated for postmenopausal women.[22] Fulvestrant is not recommended by NICE for routine commissioning in England and Wales (TA503).[23] For people whose disease is life-threatening or requires early relief of symptoms, or when endocrine based therapy options have been exhausted, CG81 recommends chemotherapy.[18] For patients who progress on CDK 4/6 inhibitors in combination with an AI as first-line therapy, second-line options include: • Everolimus + exemestane[24] • Alpelisib and fulvestrant, where a patient also has a PIK3CA mutation[25] • Endocrine monotherapy[18]	

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		• Chemotherapy[18] Where HR+, HER2- locally advanced or metastatic breast cancer patients have failed endocrine therapy in the first-line setting without receiving a CDK4/6 inhibitor, NICE recommends the use of a CDK4/6 inhibitor with fulvestrant[26–28] (when exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor). Everolimus + exemestane can also be used in this instance.[24]. Fulvestrant monotherapy is not recommended for use following anti-estrogen therapy, as an alternative to aromatase inhibitors (NICE technology appraisal 239).[29] Subsequent treatment options also include chemotherapy for some people.[18] **References** 6. CancerData. Last accessed: 09/01/2023. https://www.cancerdata.nhs.uk/incidence_and_mortality. 7. Your Data - Nomis - Official Census and Labour Market Statistics. Last accessed: 08/31/2023. https://www.nomisweb.co.uk/query/asv2htm. 8. Early Diagnosis. Last accessed: 08/31/2023. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. 9. Survival and Incidence by Stage at Diagnosis. Last accessed: 08/31/2023. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. 10. Dewis R, Gribbin J. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. National Collaborating Centre for Cancer (UK); 2009. 11. Hermida-Prado F, Jeselsohn R. The ESR1 Mutations: From Bedside to Bench to Bedside. Cancer Research. 2021;81(3):537–538. https://doi.org/10.1158/0008-5472.CAN-20-4037. 12. Toy W, Shen Y, Won H, et al. ESR1 ligand binding domain mutations in hormone-resistant breast cancer. Nat Genet. 2013;45(12):1439–1445. https://doi.org/10.1038/ng.2822.	

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		13. Toy W, Weir H, Razavi P, et al. Activating ESR1 mutations differentially impact the efficacy of ER antagonists. Cancer Discov. 2017;7(3):277–287. https://doi.org/10.1158/2159-8290.CD-15-1523. 14. Li S, Shen D, Shao J, et al. Endocrine-Therapy-Resistant ESR1 Variants Revealed by Genomic Characterization of Breast-Cancer-Derived Xenografts. Cell Rep. 2013;4(6):10.1016/j.celrep.2013.08.022. https://doi.org/10.1016/j.celrep.2013.08.022. 15. Jeselsohn R, Yelensky R, Buchwalter G, et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer. Clin Cancer Res. 2014;20(7):1757–1767. https://doi.org/10.1158/1078-0432.CCR-13-2332. 16. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer. Journal of Clinical Oncology. 2016. https://doi.org/10.1200/JCO.2016.67.3061. 17. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med. 2015;7(313):313ra182. https://doi.org/10.1126/scitranslmed.aac7551. 18. NICE. Advanced breast cancer: diagnosis and treatment CG81. National Institute for Health and Care Excellence; 2017. 19. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017. 20. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496. National Institute for Health and Care Excellence; 2017.	

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		21. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone Receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563. National Institute for Health and Care Excellence; 2019. 22. Breast cancer | Treatment summaries | BNF content published by NICE. Last accessed: 08/31/2023. https://bnf.nice.org.uk/treatment-summaries/breast-cancer/. 23. NICE. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer: TA503. National Institute for Health and Care Excellence; 2018. 24. NICE. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy: TA421. National Institute for Health and Care Excellence; 2016. 25. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer: TA816. National Institute for Health and Care Excellence; 2022. 26. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA725. National Institute for Health and Care Excellence; 2021. 27. NICE. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA687. National Institute for Health and Care Excellence; 2021. 28. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA836. National Institute for Health and Care Excellence; 2022. 29. NICE. Fulvestrant for the treatment of locally advanced or metastatic breast cancer: TA239. National Institute for Health and Care Excellence; 2011.	
	METUPUK	No comments	No action needed.

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	Breast Cancer Now	In terms of completeness of information, given ESR1 mutations have been highlighted as a possible subgroup to consider if the evidence allows, it would be helpful to include information about this mutation in the background information.	Comment noted. The background section has been updated to include information on ESR1 mutations.
Population	Menarini Stemline	Menarini Stemline would like to advise that the anticipated indication is as follows: "Elacestrant as monotherapy 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 at least one line of endocrine therapy including a CDK 4/6 inhibitor". Please update the wording throughout in line with the anticipated patient population. Consistent with the anticipated indication, Menarini Stemline requests that the population wording be updated as follows: 'People with hormone receptor-positive, HER2-negative, ESR1-mutated locally advanced or metastatic breast cancer that has progressed after prior endocrine therapy including a CDK 4/6 inhibitor.	Comments noted. The scope has been amended to align with the marketing authorisation of elacestrant.
	METUPUK	No comments	No action needed.
	Breast Cancer Now	*(Is the population defined appropriately?)* Yes	Comment noted. The scope has been amended to align with the marketing authorisation of elacestrant

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Subgroups	Menarini Stemline	ESR1-mutated patients are anticipated to be the licensed indication and they should therefore not to be classed as a subgroup. For the comparator alpelisib + fulvestrant the following subgroup is proposed: Mutations in ESR1 and PIK3CA (i.e., dual mutated).	Comments noted. NICE will evaluate the technology within its marketing authorisation. The company can choose to submit data for relevant subgroups if the evidence allows. A subgroup of people with mutations in both ESR1 and PIK3CA has been added.
	METUPUK	ESR1 mutation is an appropriate subgroup. Prior chemotherapy and prior fulvestrant could be considered as subgroups Level of oestrogen receptor by IHC – consider three subgroups, ER-low positive, ER-intermediate positive, ER-high	Comments noted. The committee will consider any relevant subgroups if the evidence allows. No action needed.
	Breast Cancer Now	No comments	No action needed.
Comparators	Menarini Stemline	Menarini Stemline consider several of the comparators listed in the draft scope as not appropriate based on current clinical practice: Paclitaxel and capecitabine should be removed from the scope. These are chemotherapies, and based on CG81 and the wording from the 'response to consultee and commentator comments on the draft remit and draft scope' for TA816 (alpelisib plus fulvestrant), chemotherapy 'is only offered to patients if symptoms are severe or the disease is rapidly progressive'.[18] TA816 is a relevant technology appraisal as it is for a similar population i.e., post endocrine therapy including a CDK 4/6 inhibitor.	Comments noted. In line with the marketing authorisation for elacestrant, CDK 4/6 inhibitors (abemaciclib, ribociclib and palbociclib) have been removed as comparators from the scope. Otherwise, the

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		CDK 4/6 inhibitors in combination with aromatase inhibitors are the current first-line SoC for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.[19–21] Re-challenge with CDK 4/6 inhibitors is currently not reimbursed in the UK, and therefore CDK 4/6 inhibitors (abemaciclib, ribociclib or palbociclib) in combination with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy are not appropriate comparators given that the proposed elacestrant license restricts use to patients who have previously received a CDK 4/6 inhibitor. Fulvestrant monotherapy is not routinely commissioned in NHS clinical practice (TA239).[29] It is therefore not an appropriate comparator for this appraisal and Menarini Stemline request its removal from the scope. **References** 18. NICE. Advanced breast cancer: diagnosis and treatment CG81. National Institute for Health and Care Excellence; 2017. 19. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017. 20. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496. National Institute for Health and Care Excellence; 2017. 21. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone Receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563. National Institute for Health and Care Excellence; 2019.	scope has been kept broad. The company will have the opportunity during the evaluation to outline which comparators it considers to be most relevant.

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		29. NICE. Fulvestrant for the treatment of locally advanced or metastatic breast cancer: TA239. National Institute for Health and Care Excellence; 2011.	
	METUPUK	Yes these are the most common comparators used at present.	Comments noted. In line with the marketing authorisation for elacestrant, CDK 4/6 inhibitors (abemaciclib, ribociclib and palbociclib) have been removed as comparators from the scope. Otherwise, the scope has been kept broad.
	Breast Cancer Now	We would suggest you seek input from clinical experts into this section. We recognise everolimus with exemestane or capecitabine being used after prior CDK4/6 and AI use. And for those people whose cancer is PIK3CA mutated – alpelisib with fulvestrant. As has been highlighted in other technology appraisals, whilst fulvestrant may be available in some areas, it is not approved by NICE and is not standard of care and routinely available across the NHS in England.	Comments noted. In line with the marketing authorisation for elacestrant, CDK 4/6 inhibitors (abemaciclib, ribociclib and palbociclib) have been removed as comparators from the scope. Otherwise, the scope has been kept broad.

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Outcomes	Menarini Stemline	It should be noted that for the purposes of this appraisal only outcomes specific to the mutated ESR1 cohort from EMERALD will be considered in line with the proposed license wording for elacestrant. Menarini Stemline considers the outcome measures listed in the draft scope are appropriate and comprise the important outcomes for the assessment of efficacy, health-related benefits and harms.	Comments noted. NICE will evaluate the technology within its marketing authorisation. No action needed.
	METUPUK	No comments	No action needed.
	Breast Cancer Now	*[Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No action needed.
Equality	Menarini Stemline	Menarini Stemline are not aware of any issues of inequality in the management of breast cancer in England and Wales.	Comment noted. No action needed.
	METUPUK	No comments	No action needed.
	Breast Cancer Now	No comments	No action needed.
Other considerations	Menarini Stemline	None	No action needed.
	METUPUK	An additional line of endocrine therapy may help patients remain in employment and fulfil roles as carers for children and elderly relatives.	Comment noted. No action needed.
	Breast Cancer Now	No further comments.	No action needed.

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Questions for consultation	Menarini Stemline	**Where do you consider elacestrant will fit into the existing care pathway for postmenopausal hormone receptor-positive HER2-negative advanced or metastatic breast cancer?** The proposed licensed use for elacestrant is in disease progression following a CDK 4/6 inhibitor in the locally advanced or metastatic setting. Therefore, we expect elacestrant to be an option for treating patients with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with ESR1 mutations following progression on CDK 4/6 inhibitors. Considering that most ESR1-mutations arise almost exclusively following treatment with endocrine therapy in the metastatic setting,[1, 2, 5] we anticipate that elacestrant will predominantly displace use of everolimus plus exemestane in patients who have had at least one prior endocrine therapy including a CDK 4/6 inhibitor and harbour an ESR1 mutation. **The phase 3 trial of elacestrant versus standard of care for the treatment of patients with ER+/HER2- advanced breast cancer has reported results in all patients and patients with detectable ESR1 mutations. Are ESR1 mutations routinely tested for in hormone receptor-positive HER2-negative advanced breast cancer in NHS practice?** ESR1 mutations are not routinely tested in NHS practice and will be a requirement for initiation of elacestrant according to the proposed license. Mutation testing performed on ctDNA extracted from blood specimens would need to be included in the National Genomic Test Directory. **Would elacestrant be a candidate for managed access?** At the time of writing Menarini Stemline is still assessing elacestrant as a candidate for managed access.	Comments noted. NICE will evaluate the technology within its marketing authorisation. The scope has been updated to indicate that costs associated with diagnostic testing should be included in the economic modelling.

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		Do you consider that the use of elacestrant can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** At the time of writing, analysis of the EMERALD trial data is ongoing. The extent to which elacestrant may provide significant and substantial health-related benefits that are not included in the QALY calculation is yet to be determined. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which elacestrant will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Menarini Stemline is not aware of any such factors. **References**	

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		1. Herzog SK, Fuqua SAW. ESR1 mutations and therapeutic resistance in metastatic breast cancer: progress and remaining challenges. Br J Cancer. 2022;126(2):174–186. https://doi.org/10.1038/s41416-021-01564-x. 2. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021;23(1):85. https://doi.org/10.1186/s13058-021-01462-3. 5. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med. 2015;7(313):313ra182. https://doi.org/10.1126/scitranslmed.aac7551.	
	METUPUK	Patients value precision treatments over cytotoxic chemotherapy because they generally require fewer hospital visits and help maintain a better quality of life. We do not offer an opinion on where in the treatment cycle this drug should lie. We would welcome flexibility for oncologists to deploy elacestrant according to the needs of their patient. ESR1 mutations are not routinely tested for on the NHS. However, PIK3CA mutations are tested for in this group of patients, and so adding ESR1 moves the NHS towards providing precision personalised care. Elacestrant is a good candidate for managed access. Although median PFS has been reached, landmark analysis at 12 months shows median PFS might not fully capture how the drug works in all endocrine sensitive patients. More mature data could provide information on how the drug works over a longer timeframe. Elacestrant is an oral tablet, whereas each dose of fulvestrant is two intra muscular injections, one into each buttock. This is associated with pain at the	Comments noted. The scope has been updated to indicate that costs associated with diagnostic testing should be included in the economic modelling.

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		injection site, and requires trained personnel to administer it. Most patients if given the choice would take an oral tablet. The time taken travelling to appointments, and discomfort, and for some people embarrassment, at being injected in the buttocks is unlikely to be captured by the QALY. The tie [sic] of patients to hospital schedules which can interrupt normal work and leisure time also has a negative impact on quality of life.	
	Breast Cancer Now	**The phase 3 trial of elacestrant versus standard of care for the treatment of patients with ER+/HER2- advanced breast cancer has reported results in all patients and patients with detectable ESR1 mutations. Are ESR1 mutations routinely tested for in hormone receptor-positive HER2-negative advanced breast cancer in NHS practice?** Our understanding is that ESR1 is not routinely tested for on the NHS.	Comment noted. The scope has been updated to indicate that costs associated with diagnostic testing should be included in the economic modelling.
Additional comments on the draft scope	Menarini Stemline	No further comments	No action needed.
	METUPUK	We note that the SOC treatments offered as the control arm within the Emerald trial are not standard within the NHS. However, for many patients the current treatment lines mean they will not access any selective oestrogen receptor degrader drug, depriving them of a class of therapy which could be provide them with longer disease control.	Comments noted. The committee will consider how representative the elacestrant trial evidence is to UK clinical practice during the evaluation process. No action needed.
	Breast Cancer Now	None	No action needed.