National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG113 Anastrozole | Advice Document v1.0 | October 2024

The primary prevention of breast cancer in post-menopausal people at moderate or high risk [A]

NCMAG Decision | this on-label, off-patent use is **supported**

This advice acknowledges that widespread implementation will require development of pathways for breast cancer chemoprevention services in NHSScotland.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical-effectiveness and cost-effectiveness of anastrozole in the proposed population and made a decision to support this use.

Governance arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	Scottish Cancer Genetics Group
Medicine Name	Anastrozole
Cancer type	Breast Cancer
Proposed on-label off-patent indication	Primary prevention of breast cancer in post-menopausal people at moderate or high risk.
Medicine Details	Form: film coated tablet Dose: 1mg daily, orally, for five years

Treatment marketing authorisation[A]	Anastrozole is indicated for the primary prevention of breast cancer in post-menopausal women at moderate or high risk[1].
Advice eligibility criteria	Moderate risk[B] or high risk[C] of breast cancer: • Post-menopausal • Do not have severe osteoporosis

[A] Not all manufacturers of anastrozole have a marketing authorisation for the primary prevention of breast cancer in post-menopausal women

[B] Moderate risk of breast cancer (lifetime risk of greater than 17% but less than 30% or between 3 and 8% between the ages of 40 and 50 years)

[C] High risk of breast cancer (lifetime risk of greater than 30%, or greater than 8% between the ages of 40 and 50 years)

1. Current management context

Breast Cancer incidence, symptoms, prognosis and treatment

Breast Cancer is cancer that begins in the breast; symptoms include new lump, skin changes, nipple changes, and changes in breast size, shape, or feel. It is the most commonly diagnosed cancer in the UK with approximately 5,180 new cases in Scotland in 2021[2, 3]. Broadly, breast cancer is divided into three types: Oestrogen and or Progesterone receptor (ER) positive, Human Epidermal Receptor 2 Positive (HER2), and triple-negative (neither ER nor HER2 positive). Among these, ER positive breast cancer has the best prognosis, while triple-negative has the worst[4]. In Scotland, data are available for estimated 5-year breast cancer specific survival (BCSS) based on deprivation. For ER positive, BCSS is 88% in the least deprived and 81% in the most deprived areas. For HER2 positive, BCSS is 86% in the least deprived and 66% in the most deprived areas. For triple negative, BCSS is 75% in the least deprived and 70% in the most deprived areas [5]. Treatment typically includes surgery, radiotherapy, and systemic therapy, tailored to the patient's fitness, cancer stage, and type. ER-positive breast cancer treatment often involves chemotherapy followed by at least five years of endocrine therapy and, in some cases, targeted therapy. HER2-positive treatment usually includes chemotherapy and either trastuzumab or a pertuzumab, trastuzumab combination, followed by endocrine therapy if ER-positive. Triple-negative treatment usually includes chemotherapy and may also include immunotherapy.

Risk factors for breast cancer and chemoprevention guidelines

Breast cancer is a multifactorial disease, which may involve an interaction between environmental, lifestyle, hormonal and genetic factors. A family history of breast cancer is associated with an increased risk of the disease, which escalates with the number of affected relatives and their age at diagnosis.

National Institute for Health and Care Excellence (NICE) guidelines classify individuals with a family history of breast cancer into 3 groups: those whose risk of developing breast cancer over their lifetime is similar to the general population (less than 17%), those with moderate risk (17 to 29%), or high risk (30% or greater)[6].

Chemoprevention is the use of medication to prevent cancer from occurring. Informed decision making is essential as people must understand the absolute benefit of taking a medicine, with known side effects, to prevent a disease.

Anastrozole received marketing authorisation from the MHRA in November 2023 as part of NHS England's Medicines Repurposing Programme. NICE, the National Comprehensive Cancer Network, and the American Society of Clinical Oncology recommend the use of anastrozole in post-menopausal people. NICE recommends anastrozole unless the individual has severe osteoporosis, in which case tamoxifen and raloxifene are alternative treatment options[6-8].

Pharmacology of anastrozole

Anastrozole reduces the amount of oestrogen in the body by inhibiting its production in adipose tissue, which is the main source of oestrogen in post-menopausal people. By reducing the available oestrogen in the body, anastrozole limits one of the main pathways for breast cancer growth.

2. Evidence review approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were anastrozole, moderate and high risk and breast cancer prevention. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key research study was critically appraised using the Cochrane risk of bias version 2.0 tool[9].

3. Clinical evidence review summary

Evidence overview

A placebo-controlled study of anastrozole was identified as relevant to this proposal: the International Breast Cancer Intervention study II (IBIS-II)[10, 11]. IBIS-II included 3,864 post-menopausal participants, recruited from 18 countries including the United Kingdom. The anastrozole dosing in the study is as per the licensed dosing. Details of the design, selection criteria and outcomes of the IBIS-II study are briefly described below[10, 11]. The results from the study were also used to inform the economic evaluation presented in section 7 of this advice document.

Evidence comparing anastrozole with placebo

The IBIS-II study was a phase three, double blind, randomised placebo-controlled study comparing anastrozole (1mg daily) with matched placebo in post-menopausal people at an increased risk of developing breast cancer based on a family history and at least two times greater risk than the general population[10, 11]. Patients were randomised 1:1 to receive anastrozole (n=1,920) or matching placebo (n=1,944), stratified by country. The mean age was 59.4 years, and around 34% of participants had undergone a hysterectomy. The primary outcome was the development of histologically confirmed breast cancer (either invasive or non-invasive (ductal carcinoma in situ)[10, 11].

Table 1 | Results for IBIS-II[10]

Outcomes	Events (n[%])[c]		Rate per 1,000 Person-Years		Hazard ratio (95% CI)
	Anastrozole (n=1920)	Placebo (n=1944)	Anastrozole (n=1920)	Placebo (n=1944)	
Overall breast cancer[a]	85 (4.4)	165 (8.5)	4.1	8.1	0.5 (0.4 to 0.7), p<0.0001
Invasive breast cancer	71 (3.7)	132 (6.8)	2.3	5.0	0.5 (0.4 to 0.7)
Non-invasive cancer[b]	13 (0.7)	31 (1.6)	0.6	1.5	0.4 (0.2 to 0.8)
All-cause mortality	69 (3.6)	70 (3.6)	1.7	3.4	1.0 (0.7 to 1.3)
Breast cancer mortality	2 (0.1)	3 (0.2)	0.1	0.1	0.6 (0.1 to 3.9)

[a] Primary outcome for the study
[b]Events reported as DCIS in the IBIS-II study are classified in this table as non-invasive.
[c] Analyses conducted in the intention to treat population (ITT)
Note: where the study reported the number of events and person-years of follow-up, the event rates per 1,000 person years were calculated

Summary of results from the included studies

In the IBIS-II study 74% and 77% of participants completed the full five years of treatment across the anastrozole and placebo groups respectively. Results revealed a statistically significant 49% relative risk reduction of developing breast cancer. IBIS-II also showed a 54% reduced relative risk of invasive breast cancer and a 59% reduced relative risk of non-invasive breast cancer (Table 1). The absolute risk reduction for overall breast cancer was 4.1% in the IBIS-II study. The number of people needed to be treated with anastrozole to prevent one breast cancer was 29 in the IBIS-II study. There was no evidence of a difference between groups in all-cause or breast cancer-specific mortality, however very few events accrued for these outcomes and confidence intervals are very wide for the breast cancer mortality outcome.[10]

Patient-reported outcomes

The IBIS-II study did not collect data on quality of life.

Safety evidence

This is an on-label use which has been considered by a regulator to have an acceptable safety profile. Adverse event reporting for the latest data-cut (131 months follow-up) in the IBIS-II study was limited to major adverse events, in particular cardiovascular events, and fractures: there were no differences between anastrozole and placebo. In the earlier data cut of IBIS-II, adverse events were reported during the treatment period, anastrozole was associated with higher rates of musculoskeletal events (Risk Ratio [RR] 1.10 (95% Confidence Interval [CI] 1.05 to 1.16); hot flushes or night sweats (RR 1.15 (95% CI 1.08 to 1.22); vaginal dryness (RR 1.19 (95% CI 1.03 to 1.37) and hypertension (RR 1.64 (95% CI 1.18 to 2.28)[12].

Quality assessment of the key clinical evidence

Overall, the risk of bias for the IBIS-II study was considered low. The IBIS-I trial was a well conducted double blind, randomised controlled phase three trial.

Clinical effectiveness considerations

Anastrozole, when used as a chemopreventive agent, has been shown to reduce the risk of developing breast cancer in post-menopausal women.

Results from the IBIS-II study demonstrated a statistically significant reduction in overall breast cancer (primary outcome), invasive breast cancer, and non-invasive breast cancer. The calculated number needed to treat to prevent one breast cancer is 24 in the IBIS-II study. The majority of this reduction was due to a decrease in oestrogen receptor-positive breast cancer. The data from IBIS-II is robust with low risk of bias and certainty around the estimate of treatment effect. IBIS-II had a median follow-up of nearly 11 years, and the long-term benefit of cancer prevention was maintained throughout this period.

Anastrozole has not been shown to reduce all-cause or breast cancer death, however a low number of deaths have been reported at the latest data cut.

Breast cancer death and all-cause mortality were secondary outcomes in IBIS-II, which was not designed to detect a difference between anastrozole and placebo in terms of mortality. In the IBIS-II trial deaths from breast cancer were 2/1,920 (0.16%) in the anastrozole arm and 3/1,944 (0.10%) in the placebo arm. All cause deaths were 3.6% in both arms. More mature data may help understand the impact of anastrozole on breast cancer and all-cause mortality, however the impact of breast cancer treatments may make interpretation of these results challenging. The benefits of anastrozole are primarily due to a reduction in development of oestrogen receptor-positive breast cancer, which has high survival rates.

Despite some differences the IBIS-II study results are likely to be broadly generalisable to the Scottish population

The results from the IBIS-II trial are likely generalisable to the population treated in NHS Scotland. It included many UK centres and participants, although an exact breakdown was not provided. There are differences in the criteria and methods for assessing people at increased risk of breast cancer in the IBIS-II trial, compared with the criteria in this proposal, which are based on NICE criteria. These differences in eligibility criteria, as well as the accuracy of risk assessment calculators, may reduce the generalisability of the results.

Breast cancer screening has evolved since the time of study recruitment, and practices differed in participating countries for IBIS-II, which offered mammography every two years. Current practice is for annual screening for high risk individuals aged between 40 and 65 years. For moderate risk individuals aged between 40- and 50-years annual screening is offered followed by three yearly screening from age 50. These differences may reduce the generalisability of the results.

Adverse effects

There were no increases in the rates of major adverse events for anastrozole compared to placebo at the last data cut-off. No effect was seen for major adverse events. The incidence of fractures compared to placebo were not statistically significantly increased, however, patients with severe osteoporosis were excluded from the trial, which aligns with the proposed use. For less serious

side effects, there were higher rates of arthralgia, carpal tunnel syndrome, joint stiffness, hypertension, gynaecological, and vasomotor symptoms for anastrozole compared to placebo whilst on treatment.

4. Patient group summary

We received a patient group statement from Breast Cancer Now. A representative from Breast Cancer Now was present at the NCMAG council meeting. Breast Cancer Now is a registered charity and received 0.9% pharmaceutical company funding in the past two years. The key points from the submission are summarised below:

- People experience many emotions when dealing with the complexities around risk management. Living with the knowledge that you are at an increased risk of developing breast cancer will affect everyone differently, while some might not worry or think about the prospect, others have increased worry and anxiety at the possibility.
- Breast Cancer Now highlight that additional options will give individuals more choice, it may reduce anxiety in people as they would be taking a more active role in their risk reduction.
- Many complex factors affect individual choice when considering chemopreventive medicine including side effects, how taking a tablet every day for 5 years will fit into their lifestyle, the effectiveness at risk reduction and how each medicine compares to each other.
- Living with the knowledge of an increased risk of breast cancer is an individual experience, it is important that people are provided with information relating to all available options and potential risks so that they can make an informed choice that is right for them.

5. Benefit-risk balance

This is an on-label use which the regulator has judged to have a favourable benefit-risk balance[13]. Anastrozole reduces the risk of both invasive and non-invasive breast cancer but based on the latest data, has not been shown to reduce mortality. Rates of major adverse events were not increased but there were higher rates of less serious adverse events.

6. Council review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied that the case had been made for the clinical effectiveness of anastrozole.

7. Economic evidence review summary

Economic Overview

In accordance with the proposal, this review covers the use of anastrozole for the primary prevention of breast cancer in post-menopausal people over the age of 25 years who are at moderate or high risk. A literature review of economic evaluations on this topic screened 184 studies (details of search methodology can be found in Section 2), of which only one evaluated the cost-effectiveness of chemoprevention with anastrozole in the relevant setting. The economic evaluation presented in CG164 National Institute for Health and Care Excellence (NICE) guidance (2017 update) was preferred due to its applicability to the proposal. The NICE Centre for Guidelines shared the original models related to chemoprevention under academic confidentiality. The analysis investigated the costs and consequences of anastrozole compared to no chemoprevention[6].

Type of economic evaluation

A cost-consequences analysis (CCA) was adapted based on models provided by NICE and deemed appropriate for comparing chemoprevention strategies in post-menopausal people. This revised model was used for analysis. A lifetime time horizon was employed to calculate all costs and health outcomes related to the treatment. A discount rate of 3.5% per annum was applied to all costs incurred after the first year. The results are summarised as incremental cost per breast cancer case prevented. However, the CCA analysis does not incorporate quality-adjusted life-year (QALY) gains, so for illustrative purposes, an estimate of the minimum QALY gain required per prevented breast cancer case for anastrozole to be considered cost-effective at a willingness-to-pay range of £20,000 to £30,000 per QALY is provided. Incremental adverse events and other consequences are also discussed.

Model Overview

The original model by NICE comprised of post-menopausal individuals separated into two separate models based on high risk and moderate risk of developing breast cancer[6]. Therefore, it was adapted to include costs and effects relevant to the proposed use in NHSScotland. Several changes were made to the model, which will be discussed sequentially.

The post-menopausal group was assumed to be people aged 50 years and above. This approach may not fully capture the complexity of menopause onset, which is influenced by multiple interlinked factors beyond age.

The model uses weighted risk estimates to combine high and moderate risk. The risk distribution was assumed to be 6.5% for high risk population and 93.5% for moderate risk population, based on expert opinion of clinicians in Scotland. This approach aligns with clinical data, which is separated by menopausal status rather than risk profile. The estimate of relative risk was sourced from IBIS-II study which found that anastrozole is associated with a lower incidence of invasive breast cancer [RR (95%CI): 0.51 (0.33 to 0.77)][10]. In addition, age distribution of the cohort followed the proportion of participants in the IBIS-I study[12].

Annual cost of treatment with anastrozole (1mg/day) was derived from Scottish drug tariff (accessed Jan 2024). Revisions were made to include updated costs of breast cancer treatment to account for changes in the treatment landscape since 2017, building upon the costs presented in

CG164 NICE guidance as a baseline[6]. Specifically, the costs of certain targeted therapies used in the treatment of early breast cancer (such as abemaciclib, trastuzumab, pertuzumab, trastuzumab emtansine, and pembrolizumab) were calculated using proportions derived from clinical expert opinion and NHSScotland confidential national contract prices for medicines. Currently, these medications are integrated into treatment pathways within NHSScotland. Where necessary, costs were adjusted to current prices using the health category Consumer Price Index (CPI) Index rates from the Office for National Statistics (accessed Jan 2024). Finally, age-specific mortality data for females were sourced from Office for National Statistics National Life Tables for Scotland 2020-22 (accessed Mar 2024).

Population, intervention, comparator, outcomes

As summarised above, the revised model considered moderate and high risk post-menopausal people with no personal history of breast cancer, who have no history or increased risk of thromboembolic disease or endometrial cancer, and who are eligible for chemoprevention with anastrozole. The post-menopausal group comprised people aged 50 years and above. The intervention was 1 mg of anastrozole administered once daily over a five-year period, with no chemoprevention as the comparator. In line with assumption of the original model, 50% of people discontinued anastrozole after one year of treatment, with the remaining 50% continuing treatment for the full 5 years[6]. According to a Scottish clinical expert, the higher 5-year adherence observed in the IBIS-II study (anastrozole: 74% to placebo: 77%) may be attributed to a highly selective sample of clinical trial participants who may be more motivated compared to people in real world setting. The scenarios in Table 7 and 8 were conducted to explore ±10% variation in clinical efficacy of anastrozole potentially linked to reduced adherence compared to the IBIS-II study. The primary outcome of the analysis was the cost per breast cancer case prevented. Additionally, the minimum QALY gain required per prevented breast cancer case is provided for illustrative purposes.

Cost inputs

The costs of breast cancer treatment, costs of monitoring and managing adverse events resulting from chemoprevention with anastrozole are detailed in Tables 2 – 4. The model assumed that all patients receiving chemoprevention would need two GP consultations per year while treatment was ongoing. In addition, the model assumes that every patient initiating anastrozole therapy would receive a baseline dual-energy X-ray absorptiometry (DEXA) scan because of the potential risk of diminished bone mineral density that is often associated with the administration of aromatase inhibitors (Table 3).

Table 2 | Cost components of breast cancer treatment

Category	Surgery	Radiotherapy	Chemotherapy and targeted therapy[a]	Other drugs[b]	Total costs
Cost	£ 3,506	£ 2,325	£ 16,198	£ 3,115	**£ 25,144**

[a] These include costs associated with chemotherapy drugs, chemotherapy delivery (8 cycles) and targeted therapy medicines (used in early breast cancer only) and was based on expert opinion and confidential

medicine costs. Costs related to targeted therapy administration, follow-up appointments, and toxicity management are not included.
[b] These include - pegfilgrastim, dexamethasone, ondansetron, metoclopramide and weighted average of five endocrine therapies.

Table 3 | Monitoring costs

Category	Unit cost
GP Visit	£ 94 per year
DEXA scan	£107 per year

DEXA = Dual-Energy X-ray Absorptiometry, GP = General Practitioner

Table 4 | Costs associated with adverse events of anastrozole therapy

Adverse event		Unit costs	Source
Endometrial cancer		£ 5,815	CG164 NICE guidance (Uplifted)
Thromboembolic events[a]		£ 2,137	NHS National Cost Collection Tariff 2021/22 (Uplifted)
Fractures	Hip fracture (3.2%)	£ 21,275	CG164 NICE guidance (Uplifted)
	Wrist fracture (22.1%)	£ 830	
	Vertebral fracture (2.1%)	£ 849	
	Other fractures (72.6%)	£ 2,372	

[a] Assumed as costs for deep vein thrombosis (DVT).
Refer to Table 5 for incremental adverse events compared to no chemoprevention.

Key result

In the base case, anastrozole incurs an additional cost of £21,836 per 1,000 high and moderate risk post-menopausal individuals, compared to no chemoprevention. This additional cost is driven primarily by costs of chemoprevention and monitoring consultations with GPs. However, it is partially offset by a reduction in the cost of breast cancer treatment. The total cost to prevent a single case of breast cancer in this group was determined to be £861. Chemoprevention with anastrozole in this group requires a gain of 0.03 QALYs and 0.04 QALYs per breast cancer case prevented, for £30,000 and £20,000 per QALY willingness-to-pay threshold, respectively.

Table 5 | Base case result for 1,000 post-menopausal people who received anastrozole followed over a lifetime horizon

Cost consequences results (Anastrozole versus no chemoprevention)		
Incremental cost per 1,000 people		£21,836
Breast cancer cases prevented		25
Incremental thromboembolic events per 1,000 people		1
Incremental endometrial cancer cases per 1,000 people		0
Incremental fractures per 1,000 people		4
QALY gain required per breast cancer case averted to be cost-effective for respective ICER threshold[a]	£20,000 per QALY	0.04
	£30,000 per QALY	0.03
Cost per breast cancer case prevented		**£861**

[a] Minimum QALY gain provided for illustrative purposes. An incremental gain of 1.33 QALYs per breast cancer case prevented was estimated by comparing the utility of a 50-year-old individual with breast cancer to that of an individual without breast cancer over a five-year period[5]. The calculated minimum QALY gain can be compared to this estimate to assess the likelihood of being cost-effective.

Key uncertainties

One-way sensitivity analysis (OWSA) revealed that the model is particularly sensitive to variations in the cost of breast cancer treatment and the effectiveness of chemoprevention. The cost of breast cancer treatment was varied by ±40%, taking into account the conservative breast cancer treatment cost used in the base case (Table 6). The base case relative risk of anastrozole to placebo was altered by ±10% to illustrate that the model is sensitivity to the clinical efficacy estimate (Table 7, 8). It should be noted, however, that the observed 95% confidence interval for the estimates employed in the base case exhibits a more substantial variation (Table 1).

Table 6|OWSA for cost per breast cancer case prevented by change in cost of breast cancer treatment

	Cost of breast cancer treatment	Cost per breast cancer case prevented (% change)
Sensitivity analysis 1	£15,000	£7,647 (788%)
Base case	£25,144	£861
Sensitivity analysis 2	£35,000	-£5,733 (-766%)
OWSA = one-way sensitivity analysis		

Table 7|OWSA for cost per breast cancer case prevented by change in risk reduction

	Relative risk reduction (Anastrozole versus no chemoprevention)	Cost per breast cancer case prevented (% change)
Sensitivity analysis 3	0.44	£2,975 (245%)
Base case	0.49	£861
Sensitivity analysis 4	0.54	-£851 (-199%)
OWSA = one-way sensitivity analysis		

Table 8|OWSA for minimum QALY gain required per breast cancer case by change in risk reduction

	Relative risk reduction (Anastrozole versus no chemoprevention)	QALY gain required per breast cancer case averted to be cost-effective for respective ICER threshold[a] (% change)
For £20,000 per QALY		
Sensitivity analysis 5	0.44	0.15 (245%)
Base case	0.49	0.04
Sensitivity analysis 6	0.54	-0.04 (-199%)
For £30,000 per QALY		
Sensitivity analysis 7	0.44	0.10 (245%)
Base case	0.49	0.03
Sensitivity analysis 8	0.54	-0.03 (-199%)

ICER = incremental cost-effectiveness ratio, OWSA = one-way sensitivity analysis, QALY = quality adjusted life year.

[a] Minimum QALY gain provided for illustrative purposes. An incremental gain of 1.33 QALYs per breast cancer case prevented was estimated by comparing the utility of a 50-year-old individual with breast cancer to that of an individual without breast cancer over a five-year period[5]. The calculated QALY gain can be compared to this estimate to assess the likelihood of being cost-effective.

Cost-effectiveness considerations

Generalisability

NHSScotland prices were used when available to ensure results of greater relevance. For other costs, inflation adjustments using CPI Index rates specific to health category were used (accessed Jan 2024). Further adaptations to the model (outlined in Model overview sub-section) improved the external validity to NHSScotland. The actual annual discontinuation rate of chemoprevention with anastrozole is unknown; therefore, the analysis relied on expert estimates[6]. The pathways for individuals receiving breast cancer chemoprevention in NHSScotland have not yet been established. The revised model, which aligns with the original NICE model, assumes that individuals on chemoprevention will have two GP monitoring visits per year. However, it remains unclear whether this is how chemoprevention monitoring will be implemented in NHSScotland. Excluding GP monitoring costs would lower cost per breast cancer case prevented in favour of anastrozole. The overall analysis was deemed applicable with minor constraints.

Limitations of cost consequence analysis

The key limitation of a CCA is that it does not integrate costs and outcomes into a cost-per-QALY result. It provides a disaggregated summary of costs and outcomes. Consequently, decision-makers must assess cost-effectiveness while considering treatment costs and outcomes separately. The cost per breast cancer prevented can be evaluated against a willingness-to-pay threshold. For illustrative purposes, we present an estimate of the minimum QALY gain required per prevented breast cancer case for anastrozole to be considered cost-effective within a willingness-to-pay range of £20,000 to £30,000 per QALY. In a separate analysis, NICE estimated an incremental gain of 1.33 QALYs per breast cancer case prevented by modelling the utility of a 50-year-old individual with breast cancer to that of an individual without breast cancer over a five-year period[6]. The calculated minimum QALY gain can be compared to this estimate to assess the likelihood of being cost-effective. However, it is crucial to exercise caution when using this estimate due to its inherent limitations. Notably, it was derived using mortality and utility estimates from studies conducted before 2010 and was only estimated over a five-year period.

In addition, the actual duration over which treatment effects persist remains uncertain. The IBIS-II study had a median follow-up period of 11 years[10]. The model assumes that the benefits of chemoprevention last throughout an individual's lifetime. Furthermore, the model assumes uniform reduction in breast cancer risk across all cancer types, regardless of oestrogen receptor status. Some studies suggest potential differences, which the model does not account for. However, to account for receptor status and corresponding targeted therapy, an estimated cost of early

breast cancer treatment based on clinician opinion and weighted average methodology was used in the revised model.

The model does not consider mortality rates following breast cancer or adverse events. This means that people with and without breast cancer and those with treatment related adverse events have equal mortality rates. This could potentially result in a slight overestimation of the number of adverse events in the treatment group.

The model makes a simplistic assumption that all people receiving anastrozole treatment would undergo a baseline DEXA scan. However, not all people will require a DEXA scan, which will be limited to those with, or at risk of osteoporosis. This could potentially reduce the overall cost of chemoprevention with anastrozole.

Finally, it is important to note that breast cancer treatment costs can vary based on the stage of cancer. However, this analysis does not account for the costs associated with managing metastatic disease. Moreover, costs related to targeted therapy administration, follow-up appointments, and toxicity management are not included. As a result, we have used a conservative estimate for total cost of breast cancer treatment. It is important to note that this might lead to an underestimation of the cost per breast cancer case prevented of anastrozole compared to no chemoprevention strategy, as indicated in the sensitivity analysis (Table 6).

Summary

In summary, the revised analysis, with changes to increase the relevance for NHS Scotland, was considered relevant for decision-making purposes.

8. Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council were satisfied that anastrozole is likely to be cost effective.

9. Service impact

There are currently no national pathways for the routine prescribing of breast cancer chemopreventive medicines. Implementation of the routine use of chemopreventive medicines will require development of these and it is likely to result in initial service challenges, with uncertainties surrounding the treatment pathway and medicine uptake. This challenge has been recognised and relevant stakeholders are considering approaches to the development of these pathways. A systematic review estimated that the uptake of breast cancer chemoprevention is 16%, based on published trials[14]. However, clinical experts estimate that the real-world uptake could be as low as 1.5%. Individuals who are prescribed anastrozole may require DEXA scans if they are at risk of osteoporosis. Additionally, more frequent management of hypertension may be necessary in primary care.

10.Budget impact

The change in management would increase the net medicines budget impact of management for this group. The Scottish drug tariff price of anastrozole 1 mg (28 tablets) is £2.00, with a daily dose of 1 mg, and assumed 5 years of treatment with 100% adherence. The cost per person in year 1 is expected to be £26, with a national net medicines budget impact of approximately £34,970 (based on an estimated uptake of 1,345 in the post-menopausal population). The cost per person in year 2 is expected to be £26, with a national net medicines budget impact of approximately £36,062 (based on an estimated uptake of 1,387 in the post-menopausal population). These estimates are based on the Scottish drug tariff price (accessed Jan 2024) and an annual uptake of 5%.

Separate information will be supplied to the boards to facilitate budget impact assessment.

11. Acknowledgements

NCMAG would like to acknowledge Sarah Hamilton (Genetic Counsellor) and the patient group partner, Breast Cancer Now, for their invaluable input.

NCMAG would like to acknowledge NICE and the University of Swansea for providing the health economic models.

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by
