# National Cancer Medicines Advisory Group (NCMAG) Programme

## NCMAG115 Tamoxifen | Advice Document v1.0 |October 2024

The primary prevention of breast cancer in 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 tamoxifen 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 | Tamoxifen |
| Cancer type | Breast cancer |
| Proposed off-patent and on-label indication | The primary prevention of breast cancer in people at moderate or high risk. |
| Medicine Details | Form: tablets<br>Dose: 20mg once daily, orally, for five years |
| Treatment Marketing Authorisation | The primary prevention of breast cancer in women at moderate or high risk |

| | |
|---|---|
| Advice eligibility criteria | People who are moderate risk[A] or high risk[B] for breast cancer:<br>• Pre- and peri-menopausal:<br>  ○ Do not have a history, or increased risk of thromboembolic disease.<br>  ○ Do not have a history, or risk of endometrial cancer.<br>• Post-menopausal and not suitable for anastrozole<br>  ○ Do not have a history, or increased risk of thromboembolic disease.<br>  ○ Do not have a uterus. |

[A] 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)

[B] 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[1, 2]. Broadly, breast cancer is divided into three types: Oestrogen and or Progesterone receptor (ER) positive, Human Epidermal Receptor Positive 2 (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[3]. 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.[4] 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)[5].

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

Tamoxifen is licensed as chemoprevention and its use is recommended by NICE, the National Comprehensive Cancer Network and the American Society of Clinical Oncology[3, 5, 6]. Tamoxifen is the only medicine licensed for chemoprevention for pre-menopausal people. Tamoxifen is also an option for post-menopausal people, but anastrozole is generally preferred unless the person has severe osteoporosis, undergone a hysterectomy and have no history, or increased risk of thromboembolic disease.

**Pharmacology of tamoxifen**

Tamoxifen is a Selective oestrogen Receptor Modulator (SERM) that inhibits the action of oestrogen in the breast, thereby reducing 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 tamoxifen, 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[7].

## 3. Clinical evidence review summary

### Evidence overview

Three placebo-controlled studies of tamoxifen were identified as relevant to this proposal: the International Breast Cancer Intervention study (IBIS-I); National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 and the Royal Marsden Hospital Trial[8 9, 10]. The Royal Marsden Hospital Trial is not included in this evidence review as the eight-year treatment duration does not align with the proposed treatment duration of five years. The IBIS-I and NSABP P-1 studies included large numbers of participants, ranging in size from 7,154 to 13,388 recruited from North America, Australia, New Zealand and Europe. Participants ranged in age from 35 years to over 70 years at baseline and included participants of pre- and post-menopausal status. The dosing used in these studies is as per the licensing dosing. Details of the design, selection criteria and outcomes of the IBIS-I and NSABP P-1 studies are briefly described below. The results from these studies were also used to inform the economic evaluation presented in section 7 of this advice document.

### Clinical Efficacy Evidence

### Evidence comparing tamoxifen with placebo

The IBIS-I study was a phase three, double blind, randomised placebo-controlled study comparing tamoxifen (20mg daily) with matched placebo in pre- and post-menopausal people at an increased risk of developing breast cancer. People were eligible for participation if they were at an increased risk of developing breast cancer based on a family history of breast cancer or abnormal benign breast disease. Participants were randomised 1:1 to receive tamoxifen (n=3,579) or matching placebo (n=3,575), stratified by recruitment centre. The mean age was 50.7 years, and around half of participants were aged between 45 and 54 years (54%). Just over half of the participants were post-menopausal (54%) and around 35% of participants had undergone a hysterectomy. The IBIS-I reported three data cuts with median follow ups ranging from 50 to 192 months. Data was

extracted from the final data cut (median follow up 16 years) and where not available the previous data cut was used (median follow up 96 months). The primary outcome was the occurrence of any type of breast cancer (including ductal carcinoma in situ).

The NSABP P-1 study was a multicentre, double blind randomised placebo-controlled study which compared tamoxifen (20mg daily) with placebo. People were eligible for participation if either aged older than 60 or between 35 and 59 years of age with a 5-year predicted risk for breast cancer of at least 1.66% based on the modified Gail breast cancer risk model or had to have a history of lobular carcinoma in situ (LCIS) or atypical hyperplasia. Participants were randomised to receive treatment with tamoxifen (n=6,681) or placebo (n=6,707) for five years and were stratified by age, race, history of LCIS and 5-year predicted breast cancer risk. Nearly 40% of participants were aged under 50 years, almost all participants were white (96%), more than one-third (37%) had a hysterectomy, 6% had a history of LCIS and 9% had a history of atypical hyperplasia. The average follow-up was 74 months. The primary outcome was the incidence of invasive breast cancer. The secondary outcomes were the incidence of fatal and nonfatal myocardial infarctions, the incidence of bone fractures, breast cancer mortality and adverse events.

**Table 1| Results for included tamoxifen studies [8-13]**

| Outcome | Events (n[%]) | | Rate per 1,000 Person-Years | | Risk Ratio (95% CI)[a] |
|---|---|---|---|---|---|
| | Tamoxifen | Placebo | Tamoxifen | Placebo | |
| **Overall breast cancer** | | | | | |
| IBIS-I[b] | 251 (7.0%) | 350 (9.8%) | 4.5 | 6.4 | HR 0.71 (0.61 to 0.84) |
| IBIS-I (2007 Data cut) | | | | | |
| – Pre-menopausal | 58 (1.6%) | 88 (2.5%) | 4.2 | 6.3 | 0.67 (0.47 to 0.95) |
| – Post-menopausal | 84 (2.3%) | 107 (3.0%) | 5.9 | 7.6 | 0.77 (0.57 to 1.04) |
| NSABP P-1 | 205 (3.1%) | 343 (5.1%) | 2.4 | 3.9 | 0.63 (0.53 to 0.74) |
| **Invasive breast cancer** | | | | | |
| IBIS-I | 214 (6.0%) | 289 (8.1%) | 3.9 | 5.3 | 0.73 (0.61 to 0.87) |
| NSABP P-1[b] | 145 (2.2%) | 250 (3.7%) | 3.6 | 6.3 | 0.57 (0.46 to 0.70) |
| **Non-invasive cancer**[c] | | | | | |
| IBIS-I | 35 (1.0%) | 53 (1.5%) | 0.6 | 1.0 | HR 0.65 (0.43 to 1.00) |
| NSABP P-1 | 60 (0.9%) | 93 (1.4%) | 1.5 | 2.3 | 0.63 (0.45 to 0.89) |
| **All cause mortality** | | | | | |
| IBIS-I | 182 (5.1%) | 166 (4.6%) | 3.3 | 3.0 | OR 1.10 (0.88 to 1.37) |
| NSABP P-1 | 126 (1.9%) | 114 (1.7%) | 3.1 | 2.8 | 1.10 (0.85 to 1.43) |
| **Breast cancer mortality** | | | | | |
| IBIS-I | 31 (0.9%) | 26 (0.7%) | 0.6 | 0.5 | OR 1.19 (0.68 to 2.10) |
| NSABP P-1 | 12 (0.2%) | 11 (0.2%) | 0.3 | 0.3 | 1.09 (0.48 to 2.46) |

[a] Reported as risk ratio (RR) or as stated otherwise. Ratio >1 indicates that the tamoxifen group is at increased risk and ratio <1 indicates that the tamoxifen group is at reduced risk in comparison to placebo.
[b]Primary outcome for the study.
[c]Non-invasive is described as ductal carcinoma in situ (DCIS) and lobular carcinoma in situ in the NSABP-1 study. Events reported as DCIS in the IBIS-I study are classified in this table as non-invasive.
CI: confidence intervals. OR: odds ratio; HR: hazard ratio

**Notes**: For the IBIS-I study, data are based on the most recent 2015 unless stated otherwise.[8] Where the study reported the number of events and person-years of follow-up, the event rates per 1,000 person years were calculated. Number of participants - IBIS-I study at randomisation: tamoxifen, n=3,579; placebo; n=3,575 (included in the analysis) and NSABP P-1 study at randomisation (included in the analysis): tamoxifen, n=6,681 (6,597); placebo, n= 6,707 (6,610). Follow-up times: IBIS-I study: final data cut 2015: median 16 years; 2007 data cut: median 96 months and NSABP P-1 study: average 74 months.

### Summary of results from the included studies

In the IBIS-I study nearly 68% of participants completed the full five years of treatment compared to 72% in the placebo group[11]. In the NSABP P-1 study 24% of participants discontinued therapy in the tamoxifen group compared with 20% in the placebo group[14]. Results from the IBIS-I study and NSABP P-1 study showed a statistically significant 29% and 37% reduced relative risk of developing overall breast cancer, respectively. The absolute risk reduction for overall breast cancer was calculated to be 2.8% and 2.0% in the IBIS-I and NSABP P-1 studies, respectively. The IBIS-I study reported results by menopausal status with a reduced relative risk of 33% and 23% in the pre-menopausal and the post-menopausal groups, respectively. Results from both studies also showed a reduced relative risk of developing invasive breast cancer ranging from 27% to 43% (Table 1).. In both studies, there was no evidence of a difference between groups in all-cause or breast cancer-specific mortality.

### Other evidence sources

A Cochrane review was conducted to assess the efficacy of chemopreventive medicines (two main types included: SERMs and aromatase inhibitors) directly with placebo or any other chemopreventive medicine[12]. The two types of chemopreventive medicines were also compared via network meta-analysis (NMA). The meta-analysis (included the two studies in this evidence review: IBIS-I and NSABP P-1) showed tamoxifen to reduce the relative risk of developing breast cancer compared to placebo (Risk Ratio [RR] 0.68 [95% CI 0.62 to 0.76]). The NMA revealed that aromatase inhibitors may have reduced the risk of overall breast cancer compared with tamoxifen (RR 0.67 [95% CI 0.46 to 0.98]). The planned subgroup analyses for menopausal status were not possible.

### Participant-reported outcomes

In the NSABP P-1 study, at each follow-up visit information was collected on how symptoms such as hot flushes, vaginal discharge and irregular menses impacted on health-related quality of life. Data were also collected on depression, quality of life and sexual functioning using the following instruments - Center for Epidemiological Studies, Medical Outcomes Study Short Form 36 and the Medical Outcomes Study Sexual Functioning Scale, respectively[14]. Clinically significant differences between the groups were reported for hot flushes and vaginal discharge, indicating a less favourable profile for tamoxifen[14]. There were no between group differences in the proportion of participants in each of the categories of depression. The IBIS-I 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 in the IBIS-I study was limited to major thromboembolic, cerebrovascular and cardiac events as no minor side-effects were anticipated to have occurred more than five years after completion of treatment[8]. The incidence of pre-specified adverse events were reported as a secondary aim for the NSABP P-1 study. In both studies, participants in the tamoxifen group experienced a higher incidence of thromboembolism and endometrial cancer compared to the placebo group. Data from the IBIS-I study, showed the increased risk for thromboembolism observed during treatment (RR 2.03 [95% CI 1.38 to 3.01]) reduced after discontinuation of tamoxifen (RR 1.23 [95% CI 0.71 to 2.15])[11]. Similarly, the risk for endometrial cancer was higher for tamoxifen compared with placebo during the first 5 on-treatment years (odds ratio [OR], 3.76 [95% CI 1.20 to 15.56]) but reduced on completion of treatment (OR for 5- to 10-year follow up, 0.64 [95% CI 0.21 to 1.80]; OR for ≥10-year follow-up, 1.40 [95% CI 0.38 to 5.61])[8]. The NSABP P-1 study did not group events by active treatment and post-treatment periods. The NSABP P-1 study showed people in the tamoxifen group had a lower incidence of bone fractures and a higher incidence of cataracts in comparison to people in the placebo group. In the tamoxifen group, for people aged 50 years or older the relative risk of fractures was reduced by 29% compared to the placebo group and for people aged 49 years or younger the relative risk was reduced by 53%. It may be useful to interpret these data using age as a proxy for menopausal status.

### Quality assessment of the key clinical evidence

Overall, the risk of bias for the two studies was considered low. The NSABP P-1 trial was unblinded at the time of the initial report and participants in the placebo arm were offered tamoxifen. One third of participants in the placebo group went onto receive a SERM which could bias the later results. Compliance was defined and measured differently in each of the studies. In the IBIS-I study compliance was measured by tablet counts at each 6-month follow-up visit while non-compliance for the NSABP P-1 study was defined as permanently discontinuing tamoxifen[10, 11].

### Clinical effectiveness considerations

**Tamoxifen, when used as a chemopreventive agent, has been shown to reduce the risk of developing breast cancer.**

Results from the IBIS-I and NASBP P-1 studies demonstrated a statistically significant reduction in overall breast cancer incidence (primary outcome) in the tamoxifen group, including both invasive and non-invasive types, relative to the placebo group. The IBIS-1 study estimated that the number needed to treat for 5 years with tamoxifen to prevent one breast cancer in the next 20 years was 22 (95% CI 19–26). The majority of this reduction was due to reduction in oestrogen receptor-positive breast cancer cases, with no apparent effect on oestrogen receptor-negative cancers. The data from these randomised phase III studies are robust with a low risk of bias and certainty around the estimate of treatment effect. IBIS-I had median follow up of 16 years with the long-

term benefit of cancer prevention maintained throughout this period. The benefit of tamoxifen may be underestimated due to crossover to anastrozole in the placebo arm of the NSABP-P1 trial and the use of hormone replacement therapy in the IBIS-1 trial.

**Tamoxifen has not been shown to reduce all-cause or breast cancer death**

All-cause or breast cancer deaths were secondary outcomes in the key trials, which were not designed to detect a difference between tamoxifen and placebo in terms of mortality. In the IBIS-I trial deaths from breast cancer were 0.9% (31/3,579) in the tamoxifen arm and 0.7% (26/3,575) in the placebo arm. All cause deaths were 5.1% in tamoxifen arm and 4.6% in the placebo arm. More mature data may help understand the impact of tamoxifen on all cause and breast cancer deaths. The benefits of tamoxifen are primarily due to a reduction in development of oestrogen receptor-positive breast cancer, which has high survival rates.

**The evidence is likely generalisable to the Scottish population**

The results from the IBIS-I and NSABP P-1 trials are likely generalisable to the population seen in NHS Scotland. In the IBIS-I trial, 60% of participants were recruited from the UK, 37% from New Zealand or Australia, and the remainder from the rest of Europe. In the NSABP P-1 trial, participants were recruited from the USA, although it reported that 96% of participants were white.

There are differences in the criteria and methods for assessing people at increased risk of breast cancer in the IBIS-I and NSABP P-1 studies, 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[13].

Breast cancer screening has evolved since the time of recruitment to IBIS-I, and practices differed in participating countries for IBIS-I, which offered mammography every 12 to 18 months. Current practice is for annual screening for high-risk individuals. For moderate-risk individuals aged between 40- and 50-years annual screening is offered followed by three yearly screening from 50 years.[15] These differences may reduce the generalisability of the results.

**Adverse effects**

Tamoxifen increased the risk of endometrial cancer, with the risk returning to baseline after treatment cessation. However, this risk seems to be confined to post-menopausal people, with no increase in risk for individuals under 50 years taking tamoxifen[16].

There was also an increased risk of deep vein thrombosis in people receiving tamoxifen, with the risk returning to baseline after 10 years of follow-up. An increased risk of cataracts was reported in the NSABP P-1 study and in the post-treatment period of IBIS-I.

Overall, tamoxifen increased the risk of gynaecological and vasomotor symptoms, as well as more serious side effects like deep vein thrombosis and endometrial cancer.

## 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 of 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 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[17]. Tamoxifen reduces the risk of both invasive and non-invasive breast cancer but has not been shown to reduce mortality. Important treatment-related adverse events include thrombosis, and endometrial cancer in post-menopausal people who have a uterus[18].

## 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 tamoxifen.

## 7. Economic evidence review summary

### Economic Overview

In accordance with the proposal, this review covers the use of tamoxifen for the primary prevention of breast cancer in people over the age of 25 years who are at moderate or high risk. Within the proposed use there are two broad populations: 1) pre- and peri-menopausal people, and 2) post-menopausal people. This economic evidence review examines these two populations separately.

A literature review of economic evaluations on this topic screened 184 studies (details of search methodology in Section 2), of which three evaluated the cost-effectiveness of chemoprevention with tamoxifen 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 tamoxifen compared to no chemoprevention[5].

### 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 pre-, peri- and 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, as 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 tamoxifen 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 only post-menopausal individuals separated into two separate models based on high risk and moderate risk of developing breast cancer[5]. 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 model structure was modified to include both pre- and peri-menopausal people. The post-menopausal group comprised people aged 50 years and above and those below 50 years were considered pre- and peri-menopausal. This approach may not fully capture the complexity of menopause onset, which is influenced by multiple interlinked factors beyond age. Additionally, the pre- and peri-menopausal categories were combined due to the lack of a discernible method to differentiate between them.

The weighted risk estimates were used to combine high and moderate risk. The risk distribution across the relevant population was assumed to be 6.5% for high-risk and 93.5% for moderate risk, 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 estimates of relative risk (RR) corresponding to menopausal status were sourced from the IBIS-1 study (2007 data cut) (Table 1). In addition, the baseline age distribution of the cohort followed the proportion of participants in the IBIS-1 study. Therefore, the hypothetical cohort of 1,000 individuals were distributed into high and moderate risk profiles for their respective age groups.

It was assumed that tamoxifen is not associated with increased risk of fracture or endometrial cancer in pre- and peri-menopausal people. Therefore, risk of fractures and endometrial cancer were not included for people aged less than 50 years.

Annual cost of treatment with tamoxifen (20mg/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[5]. 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 separately considered moderate and high pre- and peri-menopausal and 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 tamoxifen. The intervention was 20mg of tamoxifen 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 tamoxifen after one year of treatment, with the remaining 50% continuing treatment for the full 5 years[5]. The primary outcome of the analysis was the cost per breast cancer 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 tamoxifen are detailed in Tables 2-4. The model assumed that all people receiving chemoprevention would need two GP consultations per year while treatment was ongoing (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 from chemoprevention with tamoxifen**

| Category | Cost per person per year on tamoxifen |
|---|---|
| GP Visit | £ 94- |

GP = General Practitioner

**Table 4 | Costs associated with potential adverse events of tamoxifen**

| 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 and 6 for incremental adverse events compared to no chemoprevention.

## Key result

### Pre- and peri-menopausal

In the base case, tamoxifen incurs an additional cost of £88,276 per 1,000 high and moderate risk pre- and peri-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 £3,077. Chemoprevention with tamoxifen in this group requires a minimum gain of 0.1 QALYs and 0.2 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 pre- and peri-menopausal people who received tamoxifen followed over a lifetime horizon**

| Cost consequences results (Tamoxifen versus no chemoprevention) | | |
|---|---|---|
| Incremental cost per 1,000 people | | £88,276 |
| Breast cancer cases prevented | | 29 |
| Incremental thromboembolic events per 1,000 people | | 3 |
| Minimum QALY gain required per breast cancer case prevented to be cost-effective for respective ICER threshold[a] | £20,000 per QALY | 0.2 |
| | £30,000 per QALY | 0.1 |
| **Cost per breast cancer case prevented** | | **£3,077** |

[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.

**Post-menopausal**

In the base case, tamoxifen incurs an additional cost of £249,353 per 1,000 high and moderate risk post-menopausal individuals, compared to no chemoprevention. The total cost to prevent a single case of breast cancer in this group was determined to be £21,354. Compared to pre- and peri-menopausal group, this additional cost in post-menopausal group is driven primarily by lower reduction in risk of breast cancer and higher chances of thromboembolic events and endometrial cancer. Chemoprevention with tamoxifen in this group requires a minimum gain of 0.7 QALYs and 1.1 QALYs per breast cancer case prevented, for £30,000 and £20,000 per QALY willingness-to-pay threshold, respectively.

**Table 6 | Base case result for 1,000 post-menopausal people who received tamoxifen followed over a lifetime horizon**

| **Cost consequences results (Tamoxifen versus no chemoprevention)** | | |
|---|---|---|
| Incremental cost per 1,000 people | | £249,353 |
| Breast cancer cases prevented | | 12 |
| Incremental thromboembolic events per 1,000 people | | 3 |
| Incremental endometrial cancer cases per 1,000 people | | 1 |
| Incremental fractures per 1,000 people | | -4 |
| Minimum QALY gain required per breast cancer case prevented to be cost-effective for respective ICER threshold[a] | £20,000 per QALY | 1.1 |
| | £30,000 per QALY | 0.7 |
| **Cost per breast cancer case prevented** | | **£21,354** |

[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 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 7). The base case relative risk of tamoxifen to placebo from IBIS-I (2007 data cut) was altered by ±10% to illustrate that the model's is sensitivity to the clinical efficacy estimate (Table 8, 9). It should be noted, however, that the 95% confidence interval for the estimates employed in the base case exhibits a more substantial variation (Table 1). The extent of change in the cost per prevented case of breast cancer and the minimum QALY gain required per prevented case of breast cancer, for the intervention to be deemed cost-effective at various thresholds is presented in Tables 7 to 9.

**Table 7 | 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 | |
|---|---|---|---|
| | | Pre- and peri-menopausal (% change) | Post-menopausal (% change) |
| Sensitivity analysis 1 | £15,000 | £8,338 (171%) | £28,171 (32%) |
| Base case | £25,144 | £3,077 | £21,354 |
| Sensitivity analysis 2 | £35,000 | -£2,035 (-166%) | £14,730 (-31%) |
| OWSA = one-way sensitivity analysis | | | |

**Table 8 | OWSA for cost per breast cancer case prevented by change in risk reduction**

| | Relative risk reduction (Tamoxifen versus no chemoprevention) | | Cost per breast cancer case prevented | |
|---|---|---|---|---|
| | Pre- and peri-menopausal | Post-menopausal | Pre- and peri-menopausal (% change) | Post-menopausal (% change) |
| Sensitivity analysis 3 | 0.26 | 0.15 | £7,307 (137%) | £40,906 (92%) |
| Base case | 0.33 | 0.23 | £3,077 | £21,354 |
| Sensitivity analysis 4 | 0.40 | 0.31 | £284 (-91%) | £11,621 (-46%) |
| OWSA = one-way sensitivity analysis | | | | |

**Table 9 | OWSA for minimum QALY gain required per breast cancer case by change in risk reduction**

| | Relative risk reduction (Tamoxifen versus no chemoprevention) | | Minimum QALY gain required per breast cancer case prevented to be cost-effective for respective ICER threshold[a] | |
|---|---|---|---|---|
| | Pre- and peri-menopausal | Post-menopausal | Pre- and peri-menopausal (% change) | Post-menopausal (% change) |
| **For £20,000 per QALY** | | | | |
| Sensitivity analysis 5 | 0.26 | 0.15 | 0.38 (145%) | 2.10 (97%) |
| Base case | 0.33 | 0.23 | 0.15 | 1.07 |
| Sensitivity analysis 6 | 0.40 | 0.31 | 0.01 (-94%) | 0.57 (-47%) |
| **For £30,000 per QALY** | | | | |
| Sensitivity analysis 7 | 0.26 | 0.15 | 0.25 (145%) | 1.40 (97%) |
| Base case | 0.33 | 0.23 | 0.10 | 0.71 |
| Sensitivity analysis 8 | 0.40 | 0.31 | 0.01 (-94%) | 0.38 (-47%) |
| OWSA = One-way sensitivity analysis; ICER = incremental cost-effectiveness ratio; 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 minimum 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 tamoxifen is unknown; therefore, the analysis relied on expert estimates. 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 tamoxifen. 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 tamoxifen 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[5]. 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-I trial (2007 data cut) had a median follow-up of 96 months. 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 cost of endometrial cancer treatment was adjusted for inflation and was based on studies conducted before the 2010. Since then, advancements have likely increased the average cost of endometrial cancer treatment, thereby increasing the total cost of managing adverse events. However, due to low proportion of endometrial cancers, this is expected to have a minimal impact on overall cost per breast cancer case prevented.

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.

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 tamoxifen compared to no chemoprevention strategy, as indicated in the sensitivity analysis (Table 7).

### Summary

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

## 8. Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council were satisfied that tamoxifen 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 treatment pathways. A systematic review estimated that the uptake of breast cancer chemoprevention is 16%, based on published trials.[19] However, clinical experts estimate that the real-world uptake could be as low as 1.5%.

## 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 tamoxifen 20 mg (30 tablets) is £5.50, with a daily dose of 20 mg, and assumed 5 years of treatment with 100% adherence. The cost per person in year 1 is

expected to be £67, with a national net medicines budget impact of approximately £69,526 (based on an estimated uptake of 1,039 in the pre- and post-menopausal population combined). The cost per person in year 2 is expected to be £67, with a national net medicines budget impact of approximately £71,757 (based on an estimated uptake of 1,071 in the pre- and post-menopausal population combined). 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

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clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

**Minor document amendments**

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