Use of risk-reducing endocrine treatment in the primary prevention of breast cancer in women at high or moderate risk[1]: Referral pathway from secondary care to primary care

Background

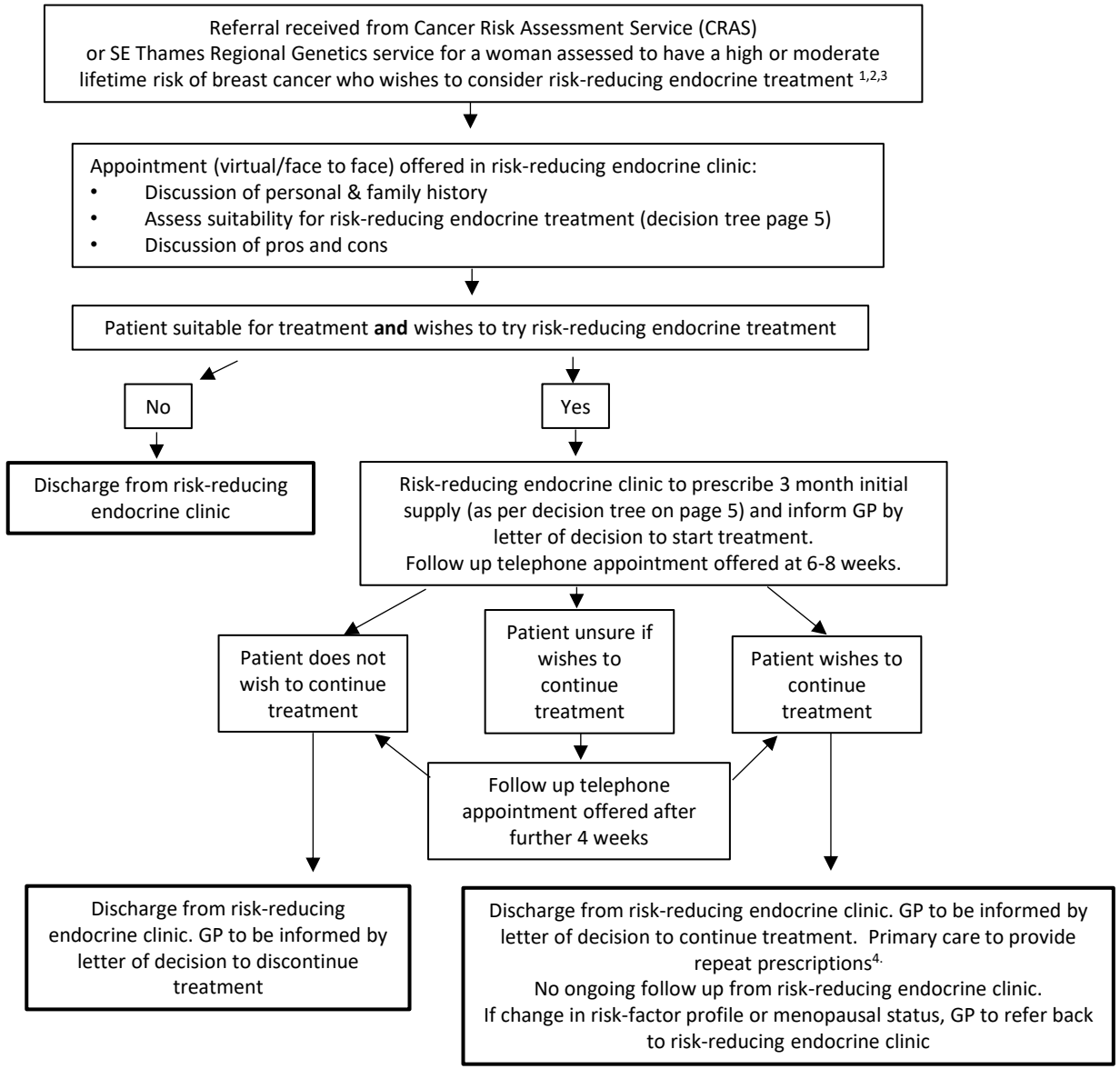
This document provides an overview of the risk-reducing endocrine treatment clinic at GSTT for women at high or moderate risk of breast cancer.

This information is intended for clinicians working in primary and secondary care to provide key information on referral pathways, treatment initiation, discharge and ongoing prescribing from primary care.

Key points for primary care:

- After assessment and counselling, the Clinical Genetics service may offer tamoxifen, anastrozole or raloxifene treatment to women at moderate or high risk of developing breast cancer.
- Tamoxifen, anastrozole (both licensed) and raloxifene (off-label) are Amber 2 in South East London for this indication. Prescribing will be initiated by the Clinical Genetics Service and transferred to primary care after the patient has had their 6-8 week review. The specialist clinic will prescribe the first 3 months.
- Treatment duration for all risk-reducing **endocrine therapy should not extend beyond 5 years.** GPs are recommended to add a treatment end-date of 5 years from commencement.
- Tamoxifen should be **discontinued 3 months before trying to conceive**
- Tamoxifen should be **discontinued 6 weeks before elective surgery**
- In the event of any queries, the Clinical Genetics team can be contacted via email at: gst-tr.geneticsreferrals@nhs.net. This email inbox is monitored 9am-5pm on Monday to Friday. Please allow up to 48 hours for a response. Patients can be referred back to the clinic if an alternative medication needs to be considered or in the event of prolonged interruption of treatment.

These guidelines have been adapted from the Greater Manchester Cancer Alliance Breast Cancer Risk Reducing Endocrine Therapy Algorithm V 2.0
https://gmcancer.org.uk/cancer-pathway-boards/breast/endocrine-therapy/#endocrinetherapytoolkit



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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

Use of tamoxifen in the primary prevention of breast cancer in women at high or moderate risk – information for primary care

Tamoxifen has been shown to reduce the chance of invasive breast cancer developing in women at increased risk due to a family history of breast cancer by around 40%. Tamoxifen is a selective oestrogen receptor modulator which exerts an anti-oestrogen effect in breast tissue, which reduces the chance of oestrogen-receptor positive breast cancers developing. Tamoxifen has no effect on oestrogen-receptor negative breast cancers.

Tamoxifen is recommended by NICE as primary prevention in pre-menopausal women with no personal history of breast cancer, who are assessed to have a high or moderate lifetime risk of developing breast cancer and who wish to take steps to reduce their future risk. This is also known as 'chemoprevention.' Options to manage an increased breast cancer risk also include additional breast surveillance (which is offered alongside tamoxifen treatment), and some women with a lifetime breast cancer risk ≥ 30% may opt to have a risk-reducing bilateral mastectomy (RRBM). Tamoxifen is not offered to women at high risk of breast cancer who have undergone a RRBM.

Suitability for tamoxifen use is assessed in secondary care or in a specialist genetics clinic. As part of the assessment, women will be advised that many who take tamoxifen will not benefit from treatment and treatment has not been shown to affect mortality from breast cancer. NICE has produced patient decision-aids for patients considering taking tamoxifen.

Prescribing route

- Prescribing will be initiated in the risk-reducing endocrine prescribing clinic (run by GSTT Clinical Genetics service)
- Patients will be provided with an initial 3 month supply.
- Primary care will be requested to prescribe ongoing supplies after the initial 3 months, in those who wish to continue treatment
- Patients will be offered a follow up telephone appointment after 6-8 weeks, after which they will either be discharged to primary care, or one further follow up appointment (after 4 weeks) may be offered and then discharged to primary care.
- Tamoxifen is prescribed at 20mg once daily, by mouth for 5 years.

Contraindications (refer to SPC or BNF for detailed information)

- Pregnancy (or trying to conceive)
- Breastfeeding
- History of DVT or PE
- History of endometrial cancer
- Concurrent use of coumarin-type anticoagulant therapy or HRT

Side effects (refer to SPC or BNF for detailed information)

- Common: Hot flushes, sweats, nausea, abnormal vaginal bleeding, vaginal discharge, vaginal dryness, leg cramps, increase in size of uterine fibroids and increase in size of ovarian cysts.
- Less common: Headaches, increased risk of DVT and PE. Increased risk of endometrial cancer in post-menopausal women.

Monitoring & follow up arrangements

- No routine monitoring is required. Treatment duration should not extend beyond 5 years.
- Tamoxifen carries an increased risk of thromboembolism and should be stopped 6 weeks before elective surgery. Instructions to discontinue tamoxifen will be discussed with patients in the risk-reducing endocrine clinic and in writing in their post-clinic letter. Consider interrupting treatment in the event of illness or prolonged immobility (ideally 3 days before immobilisation occurs). Treatment can be restarted once the initiating illness is resolved and full mobility is restored. Patients may restart tamoxifen post surgery once they are fully mobile.
- Tamoxifen should be stopped 3 months before trying to conceive. Women should be advised to use effective contraception during treatment with tamoxifen. Hormone-based contraception (oral contraceptive pill, contraceptive injection or implant) should not be used in conjunction with tamoxifen. The clinic may consider delaying risk-reducing endocrine therapy for women who have not completed their family. Instructions to discontinue tamoxifen will be discussed with patients in the risk-reducing endocrine clinic and in writing in their post-clinic letter.
- Tamoxifen may lead to changes in the endometrium including hyperplasia, polyps and endometrial cancer (in post-menopausal women). Prompt investigation of abnormal vaginal bleeding, discharge and pelvic pain/discomfort in women is recommended in women with current or prior history of tamoxifen use.

In the event of any queries, the Clinical Genetics team can be contacted via email at: gst-tr.geneticsreferrals@nhs.net

Use of anastrozole in the primary prevention of breast cancer in post-menopausal women at high or moderate risk – information for primary care

Anastrozole has been shown to reduce the chance of invasive breast cancer developing in women at increased risk due to a family history of breast cancer by around 50%. Anastrozole is an aromatase inhibitor which reduces peripheral oestrogen production, which in turn reduces the chance of oestrogen-receptor positive breast cancers developing. It has no effect on oestrogen-receptor negative breast cancers.

Anastrozole is recommended by NICE as primary prevention in post-menopausal women with no personal history of breast cancer, who are assessed to have a high or moderate lifetime risk of developing breast cancer and who wish to take steps to reduce their future risk. This is known as 'chemoprevention.' Options to manage an increased breast cancer risk also include additional breast surveillance (offered alongside anastrozole treatment), and some women with a lifetime breast cancer risk ≥ 30% may opt to have a risk-reducing bilateral mastectomy (RRBM). Anastrozole is not offered to women at high risk of breast cancer who have undergone a RRBM.

Suitability for anastrozole use is assessed in secondary care or in a specialist genetics clinic. As part of the assessment, women will be advised that many women who take anastrozole will not benefit from treatment and treatment has not been shown to affect mortality from breast cancer. NICE has produced patient decision-aids for patients considering taking anastrozole.

Prescribing route

- Prescribing will be initiated in the risk-reducing endocrine prescribing clinic (run by GSTT Clinical Genetics service)
- Patients will be provided with an initial 3 month supply.
- Primary care will be requested to prescribe ongoing supplies after the initial 3 months, in those who wish to continue treatment
- Patients will be offered a follow up telephone appointment after 6-8 weeks, after which they will either be discharged to primary care, or one further follow up appointment (after 4 weeks) may be offered and then discharged to primary care.
- Anastrozole is prescribed at 1mg once daily, by mouth for 5 years.

Contraindications (refer to SPC or BNF for detailed information)

- Pre-menopausal women
- Severe osteoporosis (T score less than or equal to -4SD)
- Concurrent use of tamoxifen or hormonal replacement therapy
- Severe renal impairment
- Severe hepatic disease

Side effects (refer to SPC or BNF for detailed information)

- Common: Menopausal symptoms, hot flushes, joint aches/stiffness, vaginal dryness, headache
- Increased risk of osteoporosis and may increase fracture risk
- Increased risk of raised cholesterol

Monitoring & follow up arrangements

- Treatment duration should not extend beyond 5 years.
- Bone density: Patients who are commenced on risk-reducing anastrozole should have a bone density scan within 3 months of commencing treatment. This will be organised by the risk-reducing endocrine clinic.
    - If the T-score is within normal limits, no treatment is required and no further bone density scan is needed.
    - If the T-score is between -1 and -2, the GP should start vitamin D and calcium supplementation and repeat the bone density scan in 2 years.
    - If the T-score is between -2 and -4, the GP should start oral bisphosphonates in addition to vitamin D and calcium, and repeat the bone density scan in 2 years.
    - If the T-score is below -4, anastrozole should be discontinued and the patient referred back to the family history clinic for discussion of raloxifene or tamoxifen. The GP should still ensure the patient is prescribed vitamin D and calcium supplementation and bisphosphonates.

In the event of any queries, the Clinical Genetics team can be contacted via email at: gst-tr.geneticsreferrals@nhs.net

Use of raloxifene in the primary prevention of breast cancer in post-menopausal women at high or moderate risk – information for primary care

Raloxifene reduces the chance of invasive breast cancer developing in women at increased risk due to a family history of breast cancer. Raloxifene is a selective oestrogen receptor modulator which exerts an anti-oestrogen effect in breast tissue, which reduces the chance of oestrogen-receptor positive breast cancers developing. Raloxifene has no effect on oestrogen-receptor negative breast cancers.

Raloxifene is recommended by NICE as an off-label indication for primary prevention in post-menopausal women with no personal history of breast cancer, who are assessed to have a high or moderate lifetime risk of developing breast cancer and who wish to take steps to reduce their future risk. This is known as 'chemoprevention.' Raloxifene is considered in post-menopausal women in whom anastrozole is unsuitable. Options to manage an increased breast cancer risk also include additional breast surveillance (which is offered alongside raloxifene treatment), and some women with a lifetime breast cancer risk ≥ 30% may opt to have a risk-reducing bilateral mastectomy (RRBM). Raloxifene is not offered to women at high risk of breast cancer who have undergone a RRBM.

Suitability for raloxifene use is assessed in secondary care or in a specialist genetics clinic. As part of the assessment, women will be advised that many women who take raloxifene will not benefit from treatment and treatment has not been shown to affect mortality from breast cancer. NICE has produced patient decision-aids for patients considering taking raloxifene.

Prescribing route

- Prescribing will be initiated in the risk-reducing endocrine prescribing clinic (run by GSTT Clinical Genetics service)
- Patients will be provided with an initial 3 month supply
- Primary care will be requested to prescribe ongoing supplies after the initial 3 months, in those who wish to continue treatment
- Patients will be offered a follow up telephone appointment after 6-8 weeks, after which they will either be discharged to primary care, or one further follow up appointment (after 4 weeks) may be offered and then discharged to primary care.
- Raloxifene is prescribed at 60mg once daily, by mouth for 5 years.

Contraindications (refer to SPC or BNF for detailed information)

- Pre-menopausal women
- History of endometrial cancer or unexplained uterine bleeding
- Personal history of venous thromboembolic events including DVT, PE and retinal vein thrombosis
- Hepatic impairment including cholestasis
- Severe renal impairment

Side effects (refer to SPC or BNF for detailed information)

- Common: Hot flushes, sweats, nausea, abnormal vaginal bleeding, vaginal discharge, vaginal dryness, leg cramps
- Less common: Headaches, increased risk of DVT and PE, visual changes and voice changes

Monitoring & follow up arrangements

- No routine monitoring is required. Treatment duration should not extend beyond 5 years.
- Raloxifene carries an increased risk of venous thromboembolism and should be stopped 6 weeks before elective surgery. Consider interrupting treatment in the event of illness or prolonged immobility (ideally 3 days before immobilisation occurs). Treatment can be restarted once the initiating illness is resolved and full mobility is restored. The risk of thromboembolism returns to normal once raloxifene is stopped.
- No increased risk for endometrial cancer has been shown with raloxifene use.

In the event of any queries, the Clinical Genetics team can be contacted via email at: gst-tr.geneticsreferrals@nhs.net

Clinical Genetics Service decision tree for risk-reducing endocrine treatment in the primary prevention of breast cancer in women at high or moderate risk[1]

Is the woman pre/peri menopausal or post-menopausal[5]?

PRE/PERI-menopausal woman breast cancer risk assessment[3]

- Lifetime breast cancer risk from age 20: less than 17%
- 10 year breast cancer risk between 40-50 years: less than 3% (less than 5% at age 50)

→ Population risk
Risk-reducing endocrine treatment not recommended

- Lifetime breast cancer risk from age 20: 17% or greater (moderate risk) or 30% or greater (high risk)
- 10 year breast cancer risk between 40-50 years: 3% or greater (moderate risk) or 8% or greater (high risk)

→ Moderate or high risk

→ Is the patient under 35 years of age?

Yes

→ Not for risk-reducing endocrine treatment at current age. Risks of endocrine treatment likely outweigh benefits.
Patient recommended to request a re-referral to risk-reducing endocrine clinic at ≥35 years.

No

→ **DVT risk-assessment:**
- Has the patient had previous DVT or PE?
- Does the patient have a first degree relative with history of DVT/PE (without precipitating factors)?
- Does the patient have a BMI greater or equal to 35?
- Does the patient have significant limitations to her mobility?
- Does the patient have significant cardiac or respiratory co-morbidity[6]?

Endometrial assessment:
- Does the patient have a family history of endometrial cancer?
- Is the patient known to have endometrial hyperplasia?

Yes to any

→ Not for tamoxifen treatment. Risks of tamoxifen treatment may outweigh benefits for this patient.
- For patients with BMI >35, advise weight loss to reduce breast cancer risk.
- For patients with other DVT/PE risks, recommend that the patient contacts family history service once post-menopausal to consider an aromatase inhibitor

No to all

→ **TAMOXIFEN**
20mg once daily for 5 years[4,9,10]

AMBER 2

POST-menopausal woman breast cancer risk assessment[3]

- Lifetime breast cancer risk from age 20: less than 17%
- 10 year breast cancer risk between 40-50 years: less than 3% (less than 5% at age 50)

→ Population risk
Risk-reducing endocrine treatment not recommended

- Lifetime breast cancer risk from age 20: 17% or greater (moderate risk) or 30% or greater (high risk)
- 10 year breast cancer risk between 40-50 years: 3% or greater (moderate risk) or 8% or greater (high risk)

→ Moderate or high risk

→ Is the patient under 70 years of age?

Yes

→ Is the patient known to have severe osteoporosis[7,8]?

Yes

→ **DVT risk assessment:**
- Has the patient had previous DVT or PE?
- Does the patient have a first degree relative with history of DVT/PE?
- Does the patient have a BMI greater or equal to 35?
- Does the patient have significant limitations to her mobility?
- Does the patient have significant cardiac or respiratory co-morbidity[6]?

Yes to any

→ Not for risk reducing endocrine medication. Risks of endocrine treatment may outweigh benefits for this patient.
- For patients with BMI >35, advise weight loss to reduce breast cancer risk.

No to all

→ Has the patient had a hysterectomy?

Yes

→ **TAMOXIFEN**
20mg once daily for 5 years[4,10]
AMBER 2

No

→ **RALOXIFENE**
(off-label) 60mg once daily for 5 years[4]
AMBER 2

No

→ **ANASTROZOLE**
1mg once daily for 5 years[4]

Assess bone mineral density[7]

AMBER 2

No

→ Not for risk-reducing endocrine treatment at current age. Risks of endocrine treatment may outweigh benefits

Use of risk-reducing endocrine treatment in the primary prevention of breast cancer in women at high or moderate risk[1]: pathway footnotes

[1]Do not offer risk-reducing endocrine medication to patients who have had bilateral mastectomy

[2]Referrals can be sent to: gst-tr.geneticsreferrals@nhs.net. GP referrals will be accepted for women who have previously been assessed by CRAS/Clinical Genetics as being at moderate or high risk of breast cancer.

[3]Lifetime breast cancer risk is assessed according to NICE CG164 definitions (below) by the Cancer Risk Assessment Service (CRAS) or Clinical Genetics service using breast cancer risk assessment guidelines:

Breast cancer risk category

	Near population risk of breast cancer	Moderate risk of breast cancer	High risk of breast cancer
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3 to 8%	Greater than 8%

[4]Treatment duration should not extend beyond 5 years for all risk-reducing endocrine treatment

[5]Consider a patient to be post-menopausal if they have had 12 continuous months without menstruation. Women under the age of 55 years, without a uterus but with at least one ovary in situ, or with a hormonal IUD (Mirena coil) in situ, will/may have no menstruation but may be pre-menopausal. In such cases, serum analysis of menopausal status will be required. Women aged 45-50 years commenced on tamoxifen treatment will be advised to request a referral back to the risk-reducing endocrine clinic once they have been amenorrhoeic for 12 months, for confirmation of menopausal status (serum LH, FSH and oestradiol). If confirmed to be post-menopausal, the patient, the risk-reducing endocrine clinic will assess if the patient can be switched to anastrozole.

[6]Consider a patient to have severe cardiac or respiratory co-morbidity if they have a medical history of: myocardial infarction, angina, cardiac failure, pacemaker, atrial fibrillation, severe COPD or other respiratory disorder that limits the activities of daily living.

[7]Severe osteoporosis is defined as T-score less than -4. Individuals with T-score greater than -4 were included in the IBIS-II trial. It is acknowledged that this definition differs from NICE CG164 definition of severe osteoporosis (T-score less than -2.5). Suitability for anastrozole will also include an assessment of prior fracture history.

[8]Women who are commenced on risk-reducing anastrozole should have a bone density scan within 3 months of commencing treatment. DEXA scans will be requested by the risk-reducing endocrine clinic or result requested from GP if DEXA performed in last 12 months. Patients for whom a DEXA scan result is awaited will be discharged to 'Patient Initiated Follow Up'. The clinic will write with the result and any recommended action for the GP. If a patient is newly identified as osteoporotic through the process of assessing suitability for risk-reducing endocrine treatment, the risk-reducing endocrine clinic will refer to secondary care if necessary for further investigations. Bone density:

- If T-score is within normal limits, no treatment is required and no further bone density scan is needed.
- If T-score is between -1 and -2, the GP should start vitamin D and calcium supplementation and repeat the bone density scan in 2 years.
- If T-score is between -2 and -4, the GP should start oral bisphosphonates in addition to vitamin D and calcium, and repeat the bone density scan in 2 years.
- If the T-score is less than -4, anastrozole should be discontinued and the patient referred back to the family history clinic for discussion of raloxifene or tamoxifen. The GP should still ensure the patient is prescribed vitamin D and calcium supplementation and bisphosphonates.

More information on the diagnosis and management of osteoporosis is available at: SEL IMOC - Adult guidelines and pathways - NHS South East London

[9]Discontinue tamoxifen 3 months before try to conceive

[10]Discontinue tamoxifen 6 weeks before elective surgery

[11]In the event of queries, the Clinical Genetics team can be contacted via email at: gst-tr.geneticsreferrals@nhs.net . Patients can be referred back to the clinic if a medication needs to be reviewed or an alternative considered due to changes in risk factors. Patients who develop new risk factors for DVT/PE whilst on tamoxifen/raloxifene should discontinue tamoxifen/raloxifene. If this is due to weight gain (BMI >35), they should be encouraged to lose weight before restarting tamoxifen/raloxifene. Pre/peri-menopausal women with DVT/PE risk factors can be re-referred back to the clinic once they are post-menopausal to consider anastrozole. Since anastrozole is the first choice treatment for post-menopausal women, re-referral of post-menopausal women on tamoxifen/raloxifene with DVT/PE risk factors is not likely to be helpful due to lack of alternatives.

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