Amber with Guidance= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.

Barnsley Hospital NHS Foundation Trust | South West Yorkshire Partnership NHS Foundation Trust | Barnsley Clinical Commissioning Group

Drug name: Anastrozole**,** tamoxifen and raloxifene for chemoprevention in familial breast cancer

Communication	When patients are seen in the Breast clinic a full discussion occurs between the breast cancer nurse and the patient. A percentage risk of the likelihood of developing breast cancer, based on family history, is given to the patient. At this point, the patient often does not want to make a decision immediately regarding chemoprevention and would prefer to consider the information provided to them by the breast cancer nurse. The breast cancer nurse would communicate with the patient's GP, advising them of the discussions that have taken place and also the possible options for chemoprevention (including drug and dose). If the patient decides that chemoprevention is the best option for them, and nothing has changed medically, then the GP could initiate treatment based on the advice of the nurse. (See Appendix A for standard paragraph to be included in GP letter for patients assessed as being moderate/high risk)
Background Information	Anastrozole, tamoxifen and raloxifene are recommended by NICE (CG164) for use as chemoprevention in familial breast cancer. Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. It inhibits the conversion of androstenedione to oestrone. Oestrone is subsequently converted to oestradiol. Reducing the circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. Tamoxifen is a non-steroidal, triphenylet hylene-based drug, which displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. It induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus. There may also be other unknown mechanisms of action. Raloxifene is a selective oestrogen receptor modulator (SERM), which has selective agonist or antagonist activities on tissues responsive to oestrogen. Raloxifene's biological actions are mediated through high affinity binding to oestrogen receptors and regulation of gene expression.
BNF therapeutic class	Anastrozole 8.4.1 Hormone responsive breast cancer Tamoxifen: 8.4.1 Hormone responsive breast cancer Raloxifene: 6.8.1 Selective oestrogen receptor modulators
Indication	Off label use for Chemoprevention in women at high or moderate risk of developing Familial breast cancer (as per NICE CG164).
Dosage and administration	**Offer** tamoxifen 20mg ONCE a day for 5 years to premenopausal women with a ***high risk*** of developing breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. **Offer** anastrozole 1mg ONCE a day for 5 years to postmenopausal women at ***high risk*** of breast cancer unless they have severe osteoporosis. For postmenopausal women at ***high risk*** of breast cancer who have severe osteoporosis or do not wish to take anastrozole:

	• offer tamoxifen for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, **or** • consider raloxifene 60mg ONCE a day for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. **<u>Consider</u>** prescribing tamoxifen 20mg ONCE a day for 5 years to women with ***moderate risk*** of developing breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. **<u>Consider</u>** anastrozole 1mg ONCE a day for 5 years to postmenopausal women at ***moderate risk*** of breast cancer unless they have severe osteoporosis. For postmenopausal women at ***moderate risk*** of breast cancer who have severe osteoporosis or do not wish to take anastrozole: • consider tamoxifen for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, or • consider raloxifene 60mg ONCE a day for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. **<u>DO NOT</u>** offer chemoprevention to women who were of ***high risk*** of breast cancer but have had a bilateral risk-reducing mastectomy. **<u>DO NOT</u>** continue chemoprevention beyond 5 years in women with no personal history of breast cancer.
Cautions **Contraindications**	• An increased risk of VTE has been demonstrated with the use of all the above drugs. • If any patient presents with VTE, chemoprevention should be stopped immediately and appropriate anti-thrombosis measures initiated. • When tamoxifen is used in combination with cytotoxic agents for the treatment of breast cancer, there is increased risk of thromboembolic events occurring. Thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy. • Stop raloxifene 3 days prior to any planned immobilisation and in acute immobility. • There is an increased risk of bone fracture with the use of anastrozole. • Stop tamoxifen at least 2 months before trying to conceive and 6 weeks before elective surgery. Anastrozole • Do not use during pregnancy or in breast-feeding women • Do not use in pre-menopausal women Tamoxifen • Tamoxifen Tablets must not be given during pregnancy (Exclude the possibility of pregnancy for premenopausal women before starting chemoprevention) Raloxifene: • avoid in women of child bearing age • avoid in severe renal or hepatic impairment and cholestasis • avoid in unexplained uterine bleeding and endometrial cancer • avoid in active or past history of DVT, PE or retinal vein thrombosis

***Amber with Guidance**= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

Adverse Drug Reactions

Frequency	Anastrozole	Tamoxifen	Raloxifene
Very common	Headache, hot flushes, nausea, rash, arthralgia/joint stiffness, asthenia, arthritis, osteoporosis	Nausea, fluid retention Vaginal bleeding, Vaginal discharge, skin rash, hot flushes, fatigue	vasodilation , Flu syndrome, nausea, vomiting, abdominal pain, dyspepsia, increased blood pressure
Common	Anorexia, hypercholesterolaemia, somnolence, carpal Tunnel Syndrome, Diarrhoea, vomiting, increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase. Hair thinning, allergic reactions, bone pain, myalgia, vaginal dryness, vaginal bleeding, sensory disturbances (including paraesthesia, taste loss and taste perversion)	Anaemia, retinopathy, leg cramp, myalgia, ischaemic cerebrovascular events, headache, light headedness, pruritus valve, endometrial changes, alopecia, vomiting, diarrhoea, constipation, thromboembolic events, uterine fibroids, hypersensitivity reactions, sensory disturbances (including paraesthesia and dysgeusia), cataracts, changes in liver enzyme, fatty liver, tumour pain, increase of serum triglyceride	leg cramps, peripheral oedema, Headache, including migraine, rash, mild breast symptoms such as pain, enlargement and tenderness
Uncommon:	Hypercalcaemia (with or without an increase in parathyroid hormone), increases in gamma-GT and bilirubin, hepatitis, urticaria, trigger finger	Endometrial cancer, thrombocytopenia, leukopenia, visual disturbances, pancreatitis, hypercalcaemia, interstitial pneumonitis, cirrhosis of the liver	VTE, thrombocytopenia fatal strokes Arterial thromboembolic reactions
Rare:	Erythema multiforme, anaphylactoid reaction, cutaneous vasculitis (including some reports of Henoch-SchÖnlein purpura)	Uterine sarcoma , tumour flare, agranulocytosis, transient falls in platelet counts, optic neuritis, corneal changes, optic neuropathy, hepatic failure, hepatocellular injury, hepatic necrosis, cutaneous vasculitis, erythema multiforme, suppression of menstruation in premenopausal women, endometriosis, cystic ovarian swelling, vaginal polyps, cholestasis, hepatitis, hypertriglyceridemia, Neutropenia, Stevens-Johnson syndrome , angioedema, bullous pemphigoid	
Vary rare:	Stevens-Johnson syndrome, angioedema	The tendency towards thrombophlebitis may increase and transient thrombocytopenia may occur. cutaneous lupus erythematosus, Porphyria cutanea tarda, radiation recall	

Monitoring

For anastrozole: due to increased risk of osteoporosis, assess bone mineral density in women with osteoporosis or at risk of osteoporosis before treatment and at regular intervals.

There are no monitoring requirements associated with the use of tamoxifen however prompt investigation will be required if a patient presents with the following symptoms:

- vaginal bleeding or discharges (including menstrual irregularities)
- pelvic pain or pressure in those who have received or are currently receiving tamoxifen

Amber with Guidance*= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

	There are no monitoring requirements for raloxifene.
Interactions	The following should be taken into consideration when prescribing regular medication for any patient who is already taking tamoxifen: • concomitant use with anticoagulants may increase INR or prothrombin time • Increased risk of VTE when given with other breast cancer treatments • P450 3A4 inducers (i.e. rifampicin) may lead to reduced tamoxifen levels • Avoid the concomitant use of some SSRI antidepressants (e.g. paroxetine & fluoxetine) due to reduced efficacy of tamoxifen. The other SSRIs do not have the same interaction and as such can be used concomitantly with tamoxifen. • Concurrent use of anastrazole and tamoxifen shows no additional clinical benefit but increases the risk of side effects. There are no notable interactions with raloxifene, however, it should not be co-administered with cholestyramine. There is no clinically significant interaction in patients treated with anastrozole and other common prescribed drugs. However, it should not be co-administrated with tamoxifen or estrogen containing therapies as it may diminish its pharmacological action.

Please refer to the relevant SPC (see links below) for full information

Contact names and details

Contact Details	Telephone number	Email
Mr S Ghosh	01226 730000	soumen.ghosh@nhs.net
Miss J Dicks (Consultant Breast Surgeon)	01226 434374	jdicks@nhs.net
Kate Widdowson (Lead Breast Care Specialist Nurse)	01226 432220	k.widdowson@nhs.net
Gillian Turrell	01226 432857	gilliansmith2@nhs.net

References

- British National Formulary 78 September 19 - March 20. Available at www.bnf.org Accessed on 12.6.20
- Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. NICE Clinical Guideline 164. June 2013, updated Nov 2019. Available at https://www.nice.org.uk/guidance/CG164 Accessed on 12.6.20
- Tamoxifen tablets. Summary of Product Characteristics. Nov 2018. Available at https://www.medicines.org.uk/emc/product/4392/smpc Accessed on 12.6.20
- Tamoxifen - managing adverse effects. NICE guidance. Dec 2014, updated Nov 2019. Available at https://cks.nice.org.uk/topics/tamoxifen-managing-adverse-effects/#!topicSummary Accessed on 19.6.20
- Evista 60mg film-coated tablets. Summary of Product Characteristics. Feb 2018. Available at https://www.medicines.org.uk/emc/medicine/595 Accessed on 19.6.20
- Anastrozole 1mg tablets. Summary of Product Characteristics. Feb 2020. Available at https://www.medicines.org.uk/emc/product/2960/smpc Accessed on 19.6.20

Development Process

This guidance has been produced by Khawer Ashfaq, Medicines Management Pharmacist, Barnsley CCG and updated by Candy Li , Medicines Management Pharmacist, Barnsley CCG (June 2020) following an AMBER-G classification status of Tamoxifen and Raloxifene in the chemoprevention in familial breast cancer by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 14th October 2020.

Amber with Guidance*= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

Appendix A: Standard paragraph to be included in GP letter for patients assessed as being moderate/high risk.

We have discussed the potential benefits and risks of chemoprevention for reducing the risk of developing a breast cancer. I have provided information leaflets on the relevant options (http://www.ukcgg.org/information-education/websites-downloads/).

Given this ladies history she would be suitable for ∗Tamoxifen 20mg OD for 5 years, ∗Anastrazole 1mg OD for 5 years or ∗raloxifene 60mg OD for 5 years based on our discussion today. She is aware to contact you if she wishes to proceed with chemoprevention and to ensure there are no past medical conditions or contraindications we are unaware of.

∗ **Delete as appropriate**