Aromatase Inhibitors

Amber- G Guidance for Aromatase Inhibitors (Anastrozole, Letrozole, Exemestane)

Introduction

Indication/Licensing information See individual SPCs for specific information for each drug. [2,3,4],

- Treatment of oestrogen receptor (ER) positive advanced breast cancer in post menopausal women (natural or induced) with no previous history of endocrine treatment or to those previously treated with tamoxifen[5].
- As an adjunct to surgery in the following patients with ER positive breast cancer:
  - Patients with a Good NPI (>2.4 but ≤3.4[6]) after 2-3 years of tamoxifen to complete 5 years total treatment*
  - Patients with a Moderate/Poor NPI (>3.4[6]) or HER2+ as an alternative to tamoxifen for 5 years.*
  - As extended adjuvant treatment in patients at continued risk of relapse following 5 years of treatment with tamoxifen (usually letrozole – continued for up to 5 years)*

* Use in conjunction with NICE guidance below:

NICE recommendations

NICE has published guideline NG101: Early and locally advanced breast cancer: diagnosis and management, which replaces the previous technology appraisal (TA112) relating to the prescribing of Aromatase inhibitors as adjuvant treatment of early oestrogen-receptor-positive breast cancer.[1]

Adjuvant endocrine therapy for invasive breast cancer:

Offer an aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated.

The NICE guideline contains new recommendations on extended endocrine therapy:

- Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at **medium or high risk** of disease recurrence and who have been taking tamoxifen for 2 to 5 years.
- Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at **low risk** of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

In postmenopausal women, switching to an aromatase inhibitor for extended therapy may be more effective at reducing recurrence than continuing with tamoxifen.

Consider that side effects of endocrine therapy will continue for additional years (for example, menopausal symptoms such as hot flushes). Also with extended use of aromatase inhibitors side effects include bone density loss, and joint and muscle pain.

Pharmacology

All act to reduce circulating oestradiol levels. Aromatase inhibitors block the conversion of androgens to oestrogens reducing the circulating levels of oestrogens.

Dosage and administration

- Oral administration. Anastrozole 1mg daily, Letrozole 2.5mg daily, Exemestane 25mg daily [2,3,4]

Adverse drug reactions, precautions, contraindications and interactions

Adverse Drug Reactions	Please see the SPC for each drug for a full list of side-effects. https://www.medicines.org.uk/emc/ Adverse events are usually mild to moderate with only few withdrawals from treatment. These were mostly due to oestrogen deprivation and include: hot flushes, nausea, fatigue, dizziness, increased sweating, vaginal dryness and hair thinning. Gastrointestinal disturbances (anorexia, nausea, vomiting and diarrhoea) have been reported with aromatase inhibitors. Also headache, rash, joint pain, hypercholesterolaemia, oedema and weight gain. Anastrozole has rarely been associated with muco-cutaneous disorders including erythema multiforme and Stevens-Johnson syndrome. Aromatase inhibitors are unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported and caution should be observed when driving or operating machinery. **Effect on bone mineral density:** As aromatase inhibitors lower circulating oestrogen levels they may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. [2,3,4]

Cautions

- The menopause should be defined biochemically in any patient where there is doubt about hormonal status.
- Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals[7] thereafter. Frequency of follow-up DEXA scan depends on baseline DEXA result and risk factors for the individual patient– the report will specifically state when (if) a follow-up DEXA is required.Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.
- **Anastrozole** and **Letrozole** contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take these medicines.
- **Exemestane**: Some manufacturers products contain sucrose and should not be administered to patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, some contain glucose and should not be administered to patients with rare glucose-galactose malabsorption and some contain methyl-p-hydroxybenzoate which may cause allergic reactions (possibly delayed).

Contraindications

Pre-menopausal women, pregnancy and breastfeeding.

Renal impairment [5]

- Anastrozole: Avoid in severe renal impairment (CrCl<20ml/min)
- Exemestane: Should be used with caution in renal impairment
- Letrozole: Should be used with caution if CrCl< 10ml/min

Hepatic Impairment [5]

- Anastrozole: Manufacturer advises use with caution in moderate to severe impairment (Child- Pugh grades B and C)[8]
- Exemestane: Should be used with caution in hepatic impairment
- Letrozole: Should be used with caution in severe hepatic impairment (Child- Pugh grade C)[8]

Drug Interactions:

- Avoid oestrogen containing therapies
- Exemestane may interact with drugs effecting cytochrome P450 3A4 enzymes E.g. efficacy may be reduced by rifampicin, anticonvulsants (phenytoin and carbamazepine) and St John's Wort.

Communication

Specialist to GP
The specialist will inform the GP when they have initiated an aromatase inhibitor. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment.

GP to specialist
If the GP has concerns over the prescribing of the drug, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
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References

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3. Exemestane. Summary of Product Characteristics. November 2018. Available at: https://www.medicines.org.uk/emc/product/3937/smpc Accessed <24.3.21>
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Development Process

This guideline was developed following an Amber-G classification of anastrozole, letrozole and exemestane. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 11th August 2021.