

Anastrozole (Arimidex) for the treatment of hormone-dependent early breast cancer in postmenopausal women

(a-NASS-tra-zole)

Summary

- The PBS listing for anastrozole changed on 1 December 2005 to include all postmenopausal women with hormone-dependent early breast cancer.
- Choose anastrozole or tamoxifen as a first-line adjuvant treatment for hormone-dependent early breast cancer.
- Anastrozole may be preferable for women at high risk of endometrial cancer, thromboembolism, cerebrovascular events or metastatic disease.
- Continue adjuvant hormonal treatment for a total of 5 years.
- Anastrozole improves disease-free survival compared with tamoxifen, but there is currently no evidence that it improves overall survival.
- Anastrozole increases the risk of fracture compared with tamoxifen.

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PBS listing

Anastrozole is listed on the PBS as a restricted benefit for the adjuvant treatment of hormone-dependent early or advanced breast cancer in postmenopausal women.¹ It is not PBS subsidised for primary prevention of breast cancer.¹

Reason for PBS listing

Anastrozole was previously listed on the PBS for postmenopausal women with hormone-dependent advanced breast cancer, or for postmenopausal women with hormone-dependent early breast cancer when tamoxifen was contra-indicated or not tolerated.¹

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended that the listing for anastrozole be extended to all postmenopausal women with hormone-dependent early breast cancer on the basis of acceptable cost effectiveness compared to tamoxifen.^{1,2} The PBAC accepted that the incremental cost is justified by the expected long-term survival benefits, which are in part due to the prevention of contralateral breast cancer.^{1,2}

Place in therapy

Anastrozole is a selective, nonsteroidal aromatase inhibitor that reduces the production of oestrogens in peripheral tissues.^{3,4} It inhibits tumour growth in postmenopausal women with hormone-dependent early (operable) or advanced (metastatic) breast cancer.^{3,4}

Tamoxifen is a selective oestrogen-receptor modulator that has been the standard adjuvant treatment for early breast cancer for many years.⁵⁻⁷ It inhibits the binding of oestrogen to receptor sites in tumours but has oestrogen-like effects on the endometrium, bone and lipids.^{3,7}

Use anastrozole or tamoxifen first line

Choose anastrozole or tamoxifen on an individual patient basis, weighing the potential absolute benefits against the possible harms of treatment.⁸ Continue adjuvant hormonal treatment for 5 years; longer treatment is the subject of ongoing studies.⁸

Evidence for anastrozole in hormone-dependent early breast cancer is based on the 5-year results of the ATAC trial, which involved 9366 postmenopausal women.⁹⁻¹¹ Anastrozole improved disease-free survival (time to local or distant recurrence, new primary breast cancer or death from any cause) compared with tamoxifen (relative risk reduction [RRR] 17%, 95% confidence interval [CI] 6% to 27%). Forty women need to be treated with anastrozole for 5 years, instead of tamoxifen, for one additional woman to remain disease-free during this time. There was no significant difference in overall survival between the anastrozole and tamoxifen groups after 5 years of follow-up.¹¹

The benefit-harm profile of tamoxifen in hormone-dependent early breast cancer has been established in meta-analyses of more than 80 000 women in randomised trials, many of whom were followed up for more than 15 years.⁵

Five-year treatment with tamoxifen reduced the relative risk of recurrence (local or distant recurrence or new primary breast cancer) by 41% (99% CI 33% to 49%) and breast cancer mortality by 34% (99% CI 24% to 44%) compared with no hormonal treatment.⁵

Tamoxifen increases the incidence of endometrial cancer, thromboembolism and stroke.^{5,6} However, it does not significantly increase the risk of death from these causes.^{5,6} The cumulative incidence of endometrial cancer with tamoxifen is small (0.1% per year) and is outweighed by a cumulative decrease in the incidence of new primary (contralateral) breast cancer (0.2% per year).⁵ Anastrozole increases the absolute risk of fracture compared with tamoxifen (see Safety issues).⁹⁻¹¹

Anastrozole may be preferred in some women

In the ATAC trial, anastrozole prolonged the time to distant recurrences compared with tamoxifen (RRR 16%, 95% CI 0% to 30%).¹¹ The incidence of contralateral breast cancer was also reduced by anastrozole compared with tamoxifen (RRR 53%, 95% CI 25% to 71%).¹¹ Distant recurrences are more common and incurable.¹² Anastrozole prevented many more distant recurrences than it did contralateral breast cancers when compared with tamoxifen.¹¹

There are, however, longer-term data on the use of tamoxifen as a first-line adjuvant treatment. The effect of tamoxifen persists for more than 15 years after initial diagnosis of breast cancer.⁵ Most of the effect on breast cancer mortality is seen after women have completed their 5 years of tamoxifen treatment (absolute risk reduction at 5 and 15 years, 3.6% and 9.2%, respectively).⁵ Long-term data beyond 5 years are currently unavailable for anastrozole.

Anastrozole is the drug of choice when tamoxifen is contra-indicated.⁸ It may be preferred for women at high risk of endometrial cancer, thromboembolism or cerebrovascular events.^{13,14} Anastrozole may also be preferred for some women at high risk of metastases.

Should women switch to anastrozole if they have remained disease free while taking tamoxifen?

There is evidence of benefit in starting anastrozole after 2 or 3 years of tamoxifen.^{15,16} However, long-term follow-up data on switching treatment are not yet available.

In the combined analysis of the ARNO 95 trial and ABCSG trial 8¹⁵, switching to anastrozole after 2 years of tamoxifen did not improve overall survival, but improved disease-free survival (time to local or distant recurrence or contralateral breast cancer) compared with 5 years of tamoxifen (RRR 40%, 95% CI 19% to 56%).

In the ITA trial¹⁶, anastrozole improved disease-free survival (time to local or distant recurrence) when initiated 2 or 3 years after tamoxifen, compared with 5 years of tamoxifen (RRR 65%, 95% CI 32% to 82%). This result may be greater than in other trials because it was a smaller trial and included women with a poorer prognosis (all node positive).¹⁶

Consider switching to anastrozole if longer treatment with tamoxifen poses an unacceptably high risk of adverse effects (see Safety issues). Start anastrozole no earlier than 2 or 3 years after starting tamoxifen, unless tamoxifen is not tolerated or disease recurs.⁸ Do not use anastrozole in combination with tamoxifen.⁹⁻¹¹

Safety issues

Anastrozole is generally well tolerated.^{3,4} Common adverse effects include hot flushes, asthenia or fatigue, nausea, headache and musculoskeletal disorders.^{3,4} Anastrozole may increase the risk of fracture compared with tamoxifen.^{3,4}

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits* and *Australian Prescriber* journal. For information about adverse drug reaction reporting, see the Therapeutic Goods Administration website (www.tga.gov.au).

Anastrozole and tamoxifen have different risks of adverse effects

In the ATAC trial the most common adverse effects reported with anastrozole or tamoxifen were hot flushes, nausea and vomiting, fatigue or tiredness, mood disturbances and arthralgia.^{9–11} Drug-related serious adverse effects were less frequent with anastrozole than with tamoxifen (4.7% vs 9.0%, respectively).¹¹ There were fewer discontinuations due to drug-related adverse effects with anastrozole than with tamoxifen (6.5% vs 8.9%).¹ However, the drugs differ in their absolute risks for individual adverse effects (Table 1).¹¹

Tamoxifen causes a greater incidence of thromboembolism and endometrial cancer because of its partial oestrogen-like activity.³ However, this action also protects against bone loss.^{3,5} Anastrozole decreases circulating oestrogen levels, which can increase the risk of fracture relative to that for tamoxifen.³ Anastrozole is not associated with the oestrogen-like adverse effects of tamoxifen.³

Use anastrozole with caution in women with osteoporosis or a history of fracture

Monitoring bone mineral density is recommended before and during treatment with anastrozole.^{3,4,8} Prophylaxis or treatment of bone loss may be necessary.^{4,8} The long-term increased risk of fracture with anastrozole, particularly of the hip, is currently unknown.⁸ However, in the ATAC trial there was no significant difference in the incidence of hip fracture between anastrozole and tamoxifen (1.2% vs 1.0%, respectively)¹¹ and total fracture rates returned to baseline levels after treatment with anastrozole was completed.¹

Dosing issues

The recommended dose of anastrozole is one 1 mg tablet taken once daily.^{3,4} Continue treatment for 5 years in postmenopausal women with early breast cancer.^{3,4,8}

Table 1: Absolute risk of adverse events reported with anastrozole and tamoxifen in the ATAC trial^{1,11}

Adverse events*	Anastrozole (%)	Tamoxifen (%)	Difference with anastrozole (%)
Hot flushes	35.7	40.9	-5.2
Arthralgia	35.6	29.4	+6.2
Fractures†	11.0	7.7	+3.3
Vaginal discharge	3.5	13.2	-9.7
Vaginal bleeding	5.4	10.2	-4.8
Hysterectomy	1.2	4.7	-3.5
Venous thromboembolic events	2.8	4.5	-1.7
Ischaemic cerebrovascular events	2.0	2.8	-0.8
Endometrial cancer	0.2	0.8	-0.6

* Reported during 5-year treatment or within 14 days of discontinuation † Included hip, spine, wrist/Colles or other fracture

Information for patients

Inform patients that anastrozole:

- is an additional hormonal treatment for early breast cancer in postmenopausal women who have hormone receptors in the cancer cells
- may be suitable for women at increased risk of endometrial cancer, blood clots or stroke, which occur rarely with tamoxifen
- may prolong the time to a recurrence of cancer and prevent more new cancers in the opposite breast compared with tamoxifen
- has not yet been proven to improve overall survival compared with tamoxifen
- causes more musculoskeletal pain and increases the risk of fracture relative to that for tamoxifen.

To help prevent bone loss and reduce the risk of fracture, advise patients to¹⁷:

- have an adequate dietary intake of calcium and vitamin D
- undertake regular exercise that includes resistance training, to improve muscle mass, strength and balance
- stop smoking and limit alcohol intake.

Refer patients to the National Breast Cancer Centre's guideline for women with early breast cancer, available at www.nbcc.org.au/resources/documents/EBC_earlyguide.pdf

Suggest or provide the Arimidex consumer medicine information (CMI) when prescribing or supplying anastrozole.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.