

Putting NICE guidance into practice

Familial breast cancer: patient decision aid user guide for healthcare professionals

**Implementing the NICE guideline on
familial breast cancer (CG164)**

Published: March 2017

This is a user guide for healthcare professionals. It accompanies [decision aids](#) for women at moderate or high risk of breast cancer to help them make informed decisions about taking chemoprevention to reduce their risk. The decision aids and user guide are based on the NICE guideline on [familial breast cancer](#) as updated in March 2017.

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The decision aids and user guide are not NICE guidance.

National Institute for Health and Care Excellence

Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT; www.nice.org.uk

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Contents

Introduction	4
Background to patient decision aids	4
The familial breast cancer patient decision aids.....	4
Licence status of anastrozole, raloxifene and tamoxifen for chemoprevention of familial breast cancer	4
Using the patient decision aids	5
Sources of data.....	6
Expert steering group.....	11
References.....	12

Introduction

This user guide gives some background to patient decision aids (PDAs) in general and the NICE PDAs for chemoprevention of familial breast cancer in particular. It gives guidance on how to use the PDAs and explains in detail the evidence used to produce them.

Background to patient decision aids

PDAs are tools designed to help people take part in making decisions about healthcare options. They provide information on the options and help people to clarify and communicate how they feel about the different features of the options. PDAs do not advise people to choose one option over another, nor are they meant to replace discussions with their healthcare professional. Instead, they prepare people to make informed, values-based decisions with their practitioner ([IPDAS collaboration 2012](#)).

Complex decisions have multiple options with features that people value differently. Sometimes the scientific evidence about options is limited. Therefore the best choice depends on the personal importance the person places on the benefits, harms and scientific uncertainties ([IPDAS collaboration 2012](#)). The values and perceptions of individual people, and their attitudes to risk, may be different from those of their healthcare professional ([Thornton 2003](#)). Using PDAs in a consultation may help to improve a person's knowledge of the options and outcomes and give them more realistic expectations ([Stacey et al. 2014](#)).

The familial breast cancer patient decision aids

These PDAs relate to chemoprevention for women who have never had breast cancer but are at moderate or high risk of it (as described in the [NICE guideline](#)). Four PDAs have been produced to cover moderate and high risk of breast cancer and menopausal status. The PDAs were developed with input from an [expert steering group](#) that included clinical experts and patient representatives.

Licence status of anastrozole, raloxifene and tamoxifen for chemoprevention of familial breast cancer

Chemoprevention of familial breast cancer with tamoxifen in premenopausal women, and with anastrozole, tamoxifen or raloxifene in postmenopausal women, is recommended as an option

in the [NICE guideline](#) (see the guideline for full details of recommendations). At the time of publication (March 2017), none of these medicines had UK marketing authorisations for this indication. The General Medical Council (GMC), in its [Prescribing guidance: prescribing unlicensed medicines](#), states that although doctors should usually prescribe licensed medicines for their licensed indications, they may prescribe unlicensed medicines when it is necessary to do so to meet the specific needs of the patient. No medicines are licensed for chemoprevention of familial breast cancer, so no licensed alternative is available. Moreover, anastrozole, tamoxifen and raloxifene are all licensed products so prescribers can be assured of the pharmaceutical quality of the products available. The GMC states that doctors must give patients sufficient information about the medicines they propose to prescribe to allow them to make an informed decision: this can be facilitated by using the PDAs. It also states that when prescribing an unlicensed medicine is supported by authoritative clinical guidance (such as a NICE guideline), it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population.

Using the patient decision aids

The [NICE guideline](#) recommends a shared approach to decision-making about chemoprevention. Relevant recommendations on good practice in shared decision-making are given in the NICE guidelines on [patient experience in adult NHS services](#) and [medicines optimisation](#).

NICE expects that the PDAs will be used by healthcare professionals within secondary care or specialist genetic clinics, who have expertise in familial breast cancer and are able to personalise the information to a particular woman's circumstances.

Healthcare professionals should explain the relevant PDA to the woman, tailoring the information to reflect her clinical circumstances as necessary. They should make it clear that, although they may have a view on the choice they would make if they were in the woman's situation, they accept that she may view the balance of risks, benefits and consequences of treatment in a different way and come to a different decision.

It is important to avoid framing information in a way that might lead to an unbalanced picture of either benefits or harms. For example, healthcare professionals should:

- tell the woman about the possible benefits from chemoprevention on risk of breast cancer, but also that no effect has been shown on risk of dying from breast cancer or any other cause
- explain to the woman that (for example) in every 1000 premenopausal women at 10% 10-year risk of breast cancer who do not take chemoprevention, 900 women would not develop breast cancer in that time and 100 would develop it. If all 1000 such women take tamoxifen for 5 years, about 30 women will avoid developing breast cancer in that time and the following 5 years (10 years in total) because they have taken tamoxifen, but about 70 women will still develop breast cancer in that time despite taking tamoxifen¹. Similar principles apply to possible harms from treatment.

Healthcare professionals should also explain that it is impossible to know what will happen to an individual woman or say whether or not she will benefit from the treatment or experience harm.

Illustrative baseline risks of breast cancer, venous thromboembolism (VTE) and endometrial cancer are given in the PDAs: the evidence for these and the effects of treatment are given in the section on [sources of data](#) below. These illustrative figures can be adapted to reflect an individual woman's baseline risk. It may be sufficient to indicate this in broad terms, but numerical estimates can also be made. For example, with a baseline VTE risk of 10 in 1000 over 5 years, the risk in tamoxifen users increases to 20 in 1000 over 5 years. If a particular woman is judged on clinical grounds to be at about half this baseline risk, her risk of VTE would increase from 5 in 1000 without treatment to 10 in 1000 on tamoxifen.

Sources of data

NICE has sought to provide numerical data that illustrate the likely benefits and risks of chemoprevention. Some assumptions and simplifications have been necessary to produce PDAs that are not too complicated to be of any use. In particular, it is not possible to illustrate graphically the effect of upper and lower confidence intervals on baseline risk, and so point estimates must be used. For relative risks that are not statistically significant at $p < 0.05$, the phrase 'has not been shown' is used in the PDAs. The primary source of information was the evidence reviewed in the 2017 [update of the NICE guideline](#), supplemented where necessary by publications derived from the studies included in the analysis and reference sources such as manufacturers' summaries of product characteristics (SPCs).

¹ See the relevant PDAs for premenopausal women at moderate risk and postmenopausal women at moderate and high risk for the equivalent benefits for such women

Baseline risk of breast cancer and benefits of treatment

The NICE guideline uses the terms 'moderate risk' and 'high risk' as follows

	Breast cancer risk category		
	Near population risk	Moderate risk	High risk ¹
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%	3–8%	Greater than 8%
¹ This group includes known <i>BRCA1</i> , <i>BRCA2</i> and <i>TP53</i> mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (<i>STK11</i>), Cowden (<i>PTEN</i>) and familial diffuse gastric cancer (E-Cadherin).			

The expert group agreed that it would be most helpful to illustrate risks over 10 years for premenopausal women at moderate and high risk, and agreed that risks of 5% and 10% would be reasonably indicative. NICE expects that healthcare professionals using the PDAs will have the expertise to be able to personalise the information to a particular woman's circumstances. A 10-year risk period was agreed as appropriate for premenopausal women because the chemoprevention option for this group is tamoxifen. There is good evidence from the IBIS 1 study ([Cuzick et al 2015](#)) that benefits from tamoxifen persist for at least 11 years after stopping treatment.

For postmenopausal women, to allow a fair comparison, a baseline risk period of 5 years was agreed because this was the median duration of follow-up in the IBIS 2 study of anastrozole ([Cuzick et al 2014](#)). Indicative risks of 2.5% and 5% for women at moderate and high risk respectively were selected as being consistent with the range of risks generated for the health economic analysis (see appendix N of the [2017 addendum](#) to the NICE guideline) and the baseline risks used in the PDAs for premenopausal women. Again it is expected that healthcare professionals using the PDAs will have the expertise to personalise the information to a particular woman's circumstances.

The relative risks for the benefits of chemoprevention on the development of invasive breast cancer are taken from the GRADE tables in appendix H of the [2017 addendum](#) to the NICE guideline. A relative risk of 0.7 was used for tamoxifen and a relative risk of 0.51 was used for

anastrozole. No direct relative risk for raloxifene versus placebo was available from the evidence review. Although the RUTH study ([Barrett-Connor et al 2006](#)), which compared raloxifene with placebo, was used as a sensitivity analysis in the health economic analysis, the expert group agreed that it would not be appropriate to use this to estimate the effects of raloxifene on the risk of invasive breast cancer in the PDAs. The RUTH study was not included in the main evidence review for the guideline update because its inclusion criteria did not meet the primary population criteria specified in the review protocol (that is, women at increased risk based on family history). Although mindful of the limitations of this approach, the expert group agreed to apply the relative risk for raloxifene versus tamoxifen from Table 8.3 of the [2013 update of the guideline](#) (relative risk 1.24) to the event rate estimated for tamoxifen: this relative risk was derived from [Vogel et al \(2010\)](#), which was also included in the 2017 update.

There was no statistically significant reduction in risk of all-cause death or of death from breast cancer with anastrozole or tamoxifen compared with placebo, or between raloxifene and tamoxifen. The expert group agreed that the PDAs should highlight the absence of any proven effect on risk of death from breast cancer.

Baseline risk of venous thromboembolism and harms from treatment

Evidence from the IBIS 1 study shows that the increased thromboembolic risk from tamoxifen is confined to the treatment period ([Cuzick et al 2007](#)). This study found a baseline risk in the placebo group of 2.4/1000 women–years for all venous thromboembolism (VTE) and 2.0/1000 women–years for VTE excluding superficial thrombophlebitis. Assuming a constant risk and that any woman experienced only one VTE event, this would give a 5-year baseline risk of 12 or 10 events per 1000 women respectively. This is consistent with the 0.9% rate of thrombosis or embolism reported in the median 5.0-year follow-up period in the IBIS 2 study ([Cuzick et al 2014](#)). An illustrative risk of 10 events per 1000 women over 5 years was agreed as suitable. The expert group agreed to add text to the PDA to explain additional risk factors for VTE; the text was based on text taken from [NHS Choices](#).

The relative risk of all VTE with tamoxifen during treatment in the IBIS 1 study was 2.03 ([Cuzick et al 2007](#)) and this was used in the PDAs, since this provides an ‘on-treatment’ relative risk and is consistent with the increase in risk stated in the SPC for [tamoxifen](#). The 2017 update to the guideline did not provide a relative risk of thromboembolism with raloxifene versus placebo, but the [2013 update of the guideline](#) states a relative risk of 1.60 for raloxifene versus placebo and

this was used in the PDAs; taken together these two relative risks are consistent with the relative risk of 1.31 for thromboembolism with tamoxifen versus raloxifene stated in the 2017 guideline update. No statistically significant increased risk of thromboembolism was seen with anastrozole in the IBIS 2 study ([Cuzick et al 2014](#)) and the SPC for [anastrozole](#) does not have any warnings related to thromboembolism, whereas such warnings are given in the SPCs for [tamoxifen](#) and [raloxifene](#). These SPCs also state the period for which tamoxifen and raloxifene should be stopped (if possible) before surgery or long-term immobility. It is assumed that that prescribers will advise women accordingly, including about risk factors for VTE and what they should do if they develop symptoms suggestive of VTE.

Baseline risk of endometrial cancer and harms from treatment

The SPC for [tamoxifen](#) warns that an increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment. In the IBIS 1 study there was an increased risk of endometrial cancer with tamoxifen, but this was confined to the treatment period ([Cuzick et al 2007](#)). Moreover, all the women affected were postmenopausal at diagnosis ([Cuzick et al 2002](#)). A systematic review ([Iqbal et al 2012](#)) of studies of tamoxifen for chemoprevention of breast cancer found no statistically significant difference between tamoxifen and control groups for the risk of endometrial cancer in women under 50 years (a proxy for menopausal status). Joint guidelines from the European Society for Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) ([Colombo et al 2016](#)) and a statement from the American College of Obstetricians and Gynecologists ([ACOG 2014](#)) agree that premenopausal women taking tamoxifen have no known increased risk of endometrial cancer. Thus, the risk of endometrial cancer was not included in the PDAs for premenopausal women. The SPC for [tamoxifen](#) advises that any woman receiving or having previously received tamoxifen who reports abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated. It is assumed that prescribers will advise women who take tamoxifen accordingly.

In the IBIS 1 study, an incidence rate for endometrial cancer of 0.38/1000 women–years was seen in the placebo group ([Cuzick 2007](#)), equivalent to 1.9 per 1000 women over 5 years

assuming constant risk; however, this was for the whole population of pre and postmenopausal women. In the general population, most cases of uterine cancer develop in postmenopausal women, with a steep increase in incidence from around the age of 50 years ([National Cancer Registration and Analysis Service 2010](#)). In the median 5.0-year follow-up period in the IBIS 2 study, the incidence of endometrial cancer was 0.26% or 2.6 per 1000 women ([Cuzick et al 2014](#)). [Cancer Research UK](#) reports an incidence rate of 59/100,000 for women aged 55–59 years, equivalent to 2.95 per 1000 women over 5 years, rising to 97/100,000 for women aged 70–74 years, equivalent to 4.9 per 1000 women over 5 years. It was agreed that an indicative rate of 3 per 1000 women over 5 years would be used in the postmenopausal PDAs.

The 2017 update to the guideline found a relative risk for all women of 2.12 (95% CI 1.47 to 3.07) for endometrial cancer with tamoxifen versus placebo. However, in the National Surgical Adjuvant Breast and Bowel Project P-1 study ([Fisher et al 1998](#)), the relative risk in women aged 49 years or younger was 1.21 (95% CI 0.41 to 3.60), whereas it was 4.01 (95% CI 1.70 to 10.90) in women aged 50 years or older. The confidence intervals for these two relative risks are wide and overlap, and both include 2.12. It was agreed that a relative risk of 2.12 would be used in the PDAs for postmenopausal women.

No statistically significant increased risk of endometrial cancer was seen with anastrozole in the IBIS 2 study ([Cuzick et al 2014](#)) and the SPC for [anastrozole](#) does not have any warnings about endometrial cancer. The 2017 update to the guideline did not provide a relative risk for endometrial cancer for raloxifene versus placebo. However, the SPC for [raloxifene](#) states that (in osteoporosis trials), after 4 years of use raloxifene did not increase the risk of endometrial cancer. Thus no increased risk of endometrial cancer was shown for anastrozole or raloxifene.

Osteoporosis and fractures

In the IBIS 2 study ([Cuzick et al 2014](#)), there was no statistically significant difference in risk of fractures with anastrozole versus placebo. However, women with evidence of severe osteoporosis (T score less than -4 or with more than 2 vertebral fractures) were excluded from the study. The SPC for [anastrozole](#) states that, because anastrozole lowers circulating oestrogen levels, it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. The SPC recommends that women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed when starting treatment and at regular intervals thereafter. The PDAs for postmenopausal women reflect this warning.

Raloxifene is licensed for treating and preventing osteoporosis in postmenopausal women. The SPC for raloxifene states that a reduction in the incidence of vertebral, but not hip fractures has been demonstrated with raloxifene. The PDAs for postmenopausal women reflect this statement. The 2017 update to the guideline found no statistically significant reduction in risk of fracture with tamoxifen versus placebo (relative risk 0.91, 95% CI 0.79 to 1.06) and the PDAs for postmenopausal women reflect this.

Other adverse effects

The most common adverse effects of anastrozole and tamoxifen are vasomotor and gynaecological in nature. Data were taken from the IBIS 2 study ([Cuzick et al 2014](#)), the RUTH study ([Barrett-Connor et al 2006](#)) and the IBIS 1 study ([Cuzick et al 2002](#)) studies for vasomotor symptoms with anastrozole, raloxifene and tamoxifen respectively. The recommendation to stop tamoxifen 2 months before conception reflects the [tamoxifen](#) SPC. More information on possible adverse effects is given in the manufacturers' patient information leaflets and these are highlighted in the PDAs.

Expert steering group

Eluned Hughes, Head of Public Health and Information, Breast Cancer Now

Judith Reeves*, Lead Breast Care Nurse, Taunton and Somerset NHS Trust

Amy Taylor*, Principal Genetic Counsellor, Cambridge University Hospitals NHS Foundation Trust

Ursula Van Mann*, Patient member

*Also a member of the update committee for the 2017 update to the NICE guideline on familial breast cancer

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