Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tamoxifen

Proprietary Product Name: Nolvadex/Nolvadex-D

Sponsor: AstraZeneca Pty Ltd

March 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
CI	Confidence interval
CMI	Consumer medicine information
DMBA	Dimethylbenzanthracene
DVT	Deep vein thrombosis
ER	Oestrogen receptor
GCP	Good Clinical Practice
HOT	Hormone Replacement Therapy Opposed by Low Dose Tamoxifen study
HR	Hazard ratio
HRT	Hormone replacement therapy
IBIS-I	International Breast Cancer Intervention Study I
ITT	Intent-to-treat
LCIS	Lobular carcinoma in situ
MI	Myocardial infarction
NHMRC	National Health and Medical Research Council
NSABP P1	National Surgical Adjuvant Breast and Bowel Project P1 study
OR	Odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
PI	Product information
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse event
SERM	Selective oestrogen-receptor modulator

Abbreviation	Meaning
STAR	NSABP Study of Tamoxifen and Raloxifene P2 study
TGA	Therapeutic Goods Administration
UK	United Kingdom
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications and Major Variation (PI) Literature Based Submission
Decision:	Approved
Date of decision:	4 April 2016
Date of entry onto ARTG	8 April 2016
Active ingredient(s):	Tamoxifen
Product name(s):	Nolvadex and Nolvadex-D
Sponsor's name and address:	AstraZeneca Pty Ltd Alma Road, North Ryde NSW 2113
Dose form(s):	Film coated tablets
Strength(s):	10 and 20 mg
Container(s):	Blister strips in container
Pack size(s):	Blister packed in strips of 10 in containers of 30.
Approved therapeutic use:	*Nolvadex/Nolvadex-D is indicated for the primary reduction of breast cancer risk in women either of moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).*
Route(s) of administration:	Oral (PO)
Dosage:	*Treatment of breast cancer* The initial dose is 20 mg once daily. In advanced breast cancer, if no response is seen, dosage may be increased to 40 mg once daily. *Primary reduction of breast cancer risk* The recommended maximum dose is 20 mg daily for 5 years.
ARTG number (s):	11232 and 11233

Product background

This AusPAR describes the application by the sponsor extend the indications of Nolvadex and Nolvadex-D containing 10 mg or 20 mg tamoxifen respectively to:

> *Nolvadex is indicated for the primary reduction of breast cancer risk in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).*

The proposed dosage for this indication is 20 mg daily.

The currently approved indications in Australia are: *Treatment of breast cancer*

Oestrogen is a natural female sex hormone and in some types of breast cancer, oestrogen can help cancer cells to grow. Tamoxifen is a nonsteroidal triphenylethylene based drug that competes with oestrogen for binding sites in target tissues such as breast and uterus. Depending on the receptor and tissue, the effect may be oestrogen like or anti oestrogen. The antagonist action is thought to account for the anti-neoplastic effect in breast cancer: in women with oestrogen receptor positive (ER-positive) breast cancer, tamoxifen reduces the risk of recurrence and death when given as adjuvant therapy for early stage disease and can provide palliation in those with metastatic disease.

Regulatory status

The following is a summary of tamoxifen inclusions on the Australian Register of Therapeutic Goods (ARTG):

Indication of treatment of breast cancer:

- Nolvadex 10 mg and 20 mg was approved by the TGA for this indication on 22 May 2007
- Tamoxifen Sandoz 10 mg and 20 mg was approved by the TGA for this indication on 26 September 2001

Palliative treatment of breast cancer:

- GenRX Tamoxifen (Tamoxifen 20 mg) was approved for this indication by the TGA on 23 February 2009

Indication of primary prevention of breast cancer:

- No tamoxifen product is currently approved for this indication by the TGA

The following is a summary of the current overseas regulatory status for Nolvadex:

Indication of treatment of breast cancer:

- Nolvadex 10 mg was first approved for marketing in the United Kingdom on 30 August 1973 and Nolvadex 20 mg was first approved on 29 January 1982.
- Nolvadex was first approved in the USA in 1977 for the indication of treatment of 'advanced breast cancer'. This was extended to 'prevention of recurrence of cancer in node-negative patients' in 1990.
- Nolvadex is currently approved in over 60 countries.

Indication of use in anovulatory fertility:

- Nolvadex and Nolvadex-D is approved for marketing for this indication by some regulatory bodies such as the UK Medicines and Healthcare products Regulatory Agency (MHRA).

Indication of primary prevention of breast cancer:

- Nolvadex is only approved for this indication in the USA; it is not approved for this use by any other jurisdiction and the sponsor does not describe any plan to submit to other jurisdictions.
- Nolvadex was approved by the Food and Drug Administration, USA, on 28 October 1998 for the indication of 'Reduction in Breast Cancer Incidence in High Risk Women' with

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- Astra Zeneca discontinued commercial supply of Nolvadex to the USA in 2006, due to dwindling market share resulting from availability of generic tamoxifen products, including Soltamox. These generic products are approved for the same indications.
- From the FDA approval letter, with attached Professional Information Brochure, approval was granted on the basis of The Breast Cancer Prevention Trial (NSABP P-1), a double blind, randomised placebo controlled trial of 13,388 high risk women who were randomised to receive tamoxifen 20 mg daily for 5 years or placebo. The trial was terminated early in 1998 and found a significant reduction in the incidence of invasive breast cancer but no reduction in overall mortality or cancer-related mortality.[1]
- Additional information regarding this indication is provided to both prescribers and patients:
  - the most recent FDA approved label for Nolvadex (2006) and the label for the currently available tamoxifen product (Soltamox) includes the following boxed warning (Figure 1):

Figure 1: Boxed warning included in the Soltamox PI as used in the USA

WARNING

For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer

Serious and life threatening events associated with Tamoxifen in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see **CLINICAL PHARMACOLOGY: Clinical Studies: Reduction in Breast Cancer Incidence in High Risk Women**). Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for Tamoxifen vs. 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for Tamoxifen vs. 0.4 for placebo)*. For stroke, the incidence rate per 1,000 women-years was 1.43 for Tamoxifen vs. 1.00 for placebo**. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for Tamoxifen vs. 0.25 for placebo**.

Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Healthcare providers should discuss the potential benefits vs. the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering Tamoxifen to reduce their risk of developing breast cancer.

The benefits of Tamoxifen outweigh its risks in women already diagnosed with breast cancer.

*Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See **WARNINGS: Effects on the Uterus: Endometrial Cancer and Uterine Sarcoma**.

See CLINICAL PHARMACOLOGY: Clinical Studies: **Table 3.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/17970s40.pdf

- The patient medication guide includes a comprehensive discussion of risks/benefits regarding this indication for Nolvadex and Soltamox.[2]

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1: Registration timeline for Submission PM-2015-02360-1-4

Description	Date
Submission dossier accepted and 1st round evaluation commenced	30 September 2015
1st round evaluation completed	25 November 2016
Sponsor provides responses on questions raised in 1st round evaluation	13 January 2016
2nd round evaluation completed	28 January 2016
Request for Advisory Committee advice and/or Delegate's Overview	2 March 2016
Sponsor's response to Delegate's Overview	16 March 2016
Advisory Committee meeting	Not applicable
Registration decision	4 April 2016
Entry onto ARTG	8 April 2016
Number of TGA working days from commencement of evaluation to registration decision*	86

*Statutory timeframe: 255 working days.

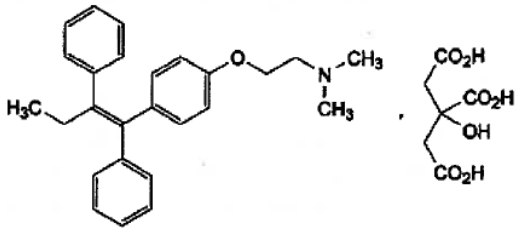
III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

[2] See Nolvadex product *http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017970s054lbl.pdf* and Soltamox product: *http://www.fda.gov/downloads/drugs/drugsafety/ucm089131.pdf* (accessed October 2015)

Drug substance (active ingredient)

Tamoxifen citrate



$C_{26}H_{29}NO$, $C_6H_8O_7$ MW: 563.6

CAS N0: 54965-244

Nolvadex (tamoxifen) is the trans-isomer of I-t4-(2-dimethylaminoethoxy) phenyll-2-diphenyl-I-butene.

Nolvadex (tamoxifen) is a non-steroidal, triphenylethylene based drug which displays a complex spectrum of oestrogen antagonist and oestrogen agonist like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antioestrogen, preventing oestrogen binding to the oestrogen receptor.

Drug product

Nolvadex is presented as white to off-white, round, biconvex film coated tablets, impressed with 'Nolvadex 10' on one face, and plain on the reverse face. Nolvadex tablets each contain tamoxifen citrate (15.2 mg) equivalent to 10 mg of tamoxifen.

Nolvadex-D is presented as white to off-white, octagonal shaped, biconvex film coated tablets, impressed with 'Nolvadex-D' on one face, and plain on the reverse face. Nolvadex-D tablets each contain tamoxifen citrate (30.4 mg) equivalent to 20 mg of tamoxifen.

Both Nolvadex and Nolvadex-D also include the following excipients: starch maize, lactose, croscarmellose sodium, gelatin, magnesium stearate, hypromellose, macrogol 300 and titanium dioxide.

Nolvadex and Nolvadex-D tablets should be protected from light and stored below 30^0C.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

A list of all the citations discussed in this section is provided in Attachment 2 under References.

Introduction

Clinical rationale

Tamoxifen is a nonsteroidal triphenylethylene based drug that competes with oestrogen for binding sites in target tissues such as breast and uterus. Depending on the receptor and tissue, the effect may be oestrogen like or anti oestrogen. The antagonist action is thought to account for the anti-neoplastic effect in breast cancer: in women with oestrogen receptor positive (ER-positive) breast cancer, tamoxifen reduces the risk of recurrence and death when given as adjuvant therapy for early stage disease and can provide palliation in those with metastatic disease. However, not all ER-positive cancers respond to tamoxifen and resistance may develop in advanced cancers.

A central anti-oestrogen action is thought to cause the hot flushes that may occur with treatment. An agonist action in the uterus is thought to be responsible for endometrial hyperplasia, vaginal discharge and increased risk of both endometrial cancer and uterine sarcoma. Other effects of tamoxifen include increased rate of venous thromboembolic events, lowering of serum cholesterol and increased risk of cataracts. Tamoxifen may also be associated with an increased incidence of arterial thromboembolism.

Tamoxifen has been in clinical use for the treatment of breast cancer since the 1970s. It has also been approved by the Food and Drug Administration (FDA), for the indication of '*Reduction in Breast Cancer Incidence in High Risk Women'* since 1998. Marketing for this indication is not approved in any other jurisdiction. Despite this, current evidence based guidelines of a number of organisations around the world recommend the use of tamoxifen in this way. These recommendations are publically available and include:

- *Cancer Council Australia* which recommends that women who are at high risk because of a very strong family history may benefit from hormones such as tamoxifen, usually administered over five years.[3]
- *Cancer Australia* which recommends that women over 35 years of age with moderate risk or women of any age with high risk of breast cancer (as determined by the online calculator provided – FRA-BOC), consider the use of medication, such as tamoxifen or raloxifene, to reduce risk of developing breast cancer. This requires careful assessment of risk and benefits in the individual case by an experienced medical professional.[4]
- *The American Society of Clinical Oncology* Clinical Practice Guideline which recommends: In women at increased risk of BC age ≥35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor (ER) –positive BC.[5]
- *The U.S. Preventive Services Task Force (USPSTF)* which recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene.[6]
- The UK *National Institute for Health and Care Excellence (NICE)* Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer Clinical Guideline (CG 164) from 2013 which

[3] Accessed November 2015 at: http://www.cancer.org.au/about-cancer/types-of-cancer/breast-cancer.html
[4] Accessed November 2015 at https://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc
[5] Accessed November 2015 at http://jco.ascopubs.org/content/31/23/2942.full
[6] Moyer V for the USPSTF Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement Ann Intern Med. 2013;159:698-708

> recommends that tamoxifen for 5 years be offered to premenopausal women at high risk of breast cancer and to postmenopausal women with or without a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer.[7]

One in 8 Australian women develop breast cancer before the age of 85 and breast cancer is the second most common cause of cancer death in Australian women. Cancer Australia estimates that 4% of the Australian female population has moderately increased risk of breast cancer (risk of breast cancer up to age 75 between 1 in 8 and 1 in 4; risk 1.5 to 3 times the population average) and that 1% are potentially high risk (risk of breast cancer up to age 75 is between 1 in 4 and 1 in 2; risk may be more than 3 times the population average).

For women at increased risk of breast cancer, apart from personal choices such as age of first birth, breastfeeding, body weight and minimising alcohol intake, the main options available to reduce this risk are bilateral mastectomy or risk reducing medications. Annual breast screening (mammograms, ultrasound, and magnetic resonance imaging) may be used to enable early detection of breast cancer but there is a concern regarding interval cancers. Bilateral mastectomy is effective at reducing breast cancer risk but is generally only offered to women at very high risk of breast cancer and, in Australia, only a minority of these women undergo the procedure. Therefore, for women whose risk is not high enough to warrant a bilateral mastectomy, or for those who choose not to undergo the surgery, risk-reducing medications is the only real option to reduce the risk of breast cancer.

A study of focus groups of Australian clinicians at Family Cancer Centres in 2009 found that barriers to the use of tamoxifen included insufficient evidence of efficacy, adverse events/side effects risks outweighing benefits, drugs not approved for this indication by regulatory authorities and cost not subsidised by the PBS.[8] The meta-analysis, by Nelson et al[9], provided in the submission, found the adverse effect profile of tamoxifen to be a barrier for women at risk. Further evidence regarding the efficacy of tamoxifen has since become available with the publishing of a meta-analysis of the use of SERMS in risk reduction of breast cancer (Cuzick 2013) and the most recent report of the 20 year follow-up of the key IBIS-1 trial (Cuzick 2015). Marketing approval of tamoxifen for the indication of risk reduction of breast cancer may improve access to this option for women with increased risk of breast cancer and may facilitate discussion of this option between the clinician and woman at risk.

Guidance

This is a Literature Based Submission. The search strategy and selection criteria used for the submission were documented by the sponsor.

Contents of the clinical dossier

Scope of the clinical dossier

The following articles and reports were submitted:

- 35 articles related to controlled studies (published between 1992 and 2015)

[7] Accessed November 2015 at: http://www.nice.org.uk/guidance/cg164/chapter/1-recommendations#risk-reduction-and-treatment-strategies
[8] Keogh L et al. Australian clinicians and chemoprevention for women at high familial risk for breast cancer. Hereditary Cancer In Clinical Practice 2009, 7:9
[9] Nelson HD, Smith MEB, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013; 158(8):604-14.

- 1 article related to uncontrolled studies (published 2003)
- 9 articles related to data from more than one study (published between 2002 and 2013)
- Nolvadex Periodic Benefit-Risk Evaluation Report (PBRER)for the period 30 April 2013 to 29 April 2014 (International birth date 30 April 1996)

Paediatric data

The submission did not include paediatric data. The current PI includes a description of a small study of tamoxifen used in 28 girls aged 2-10 years with McCune Albright Syndrome (MAS). Tamoxifen is not currently approved for this use.

Good clinical practice

The 4 randomised controlled clinical trials on which many of the publications were based were commenced prior to the implementation of the Good Clinical Practice Guideline. Documentation of ethics approval, funding source(s) and conflict of interest disclosures is provided with the publication description. In keeping with the publication dates and journal practices in the early to mid-1990s this information was not available for all publications.

Pharmacokinetics and Pharmacodynamics

The sponsor's Clinical Overview states that no new information regarding the Clinical Pharmacology is provided. The information provided in the sponsor's Clinical Overview regarding pharmacokinetics, pharmacodynamics and drug interactions has been directly sourced from the currently approved PI and is not repeated in full in this clinical evaluation.

In summary, tamoxifen is orally administered; absorbed from the gastro-intestinal tract (site and extent unknown, bioavailability unknown); peak levels are seen 3 to 6 hours after administration, steady state levels are seen after approximately 4 weeks; highly protein bound (99% to albumin); metabolised in the liver with a major active metabolite; excreted slowly, mainly in the faeces, with an elimination half-life of 5 to 7 days, and 10 to 14 days for the active metabolite; interactions may be seen with coumarin type anticoagulants (increased anticoagulant effect), cytotoxic agents (increased risk of thromboembolic effects), cytochrome P40 isozyme CYP3A4 inducers (reduced tamoxifen plasma level), CYP2D6 inhibitors (reduced plasma level of the active metabolite).

Literature search strategy and selection criteria

Background

The proposed search strategy and selection criteria were provided to the TGA in March 2015. The stated intention was that the systematic literature review would assess the efficacy and safety of tamoxifen for breast cancer prevention in women at increased risk of breast cancer only. After some minor changes, a revised search strategy was approved by the TGA. The search was performed by the sponsor on April 1 2015. The submission was provided to the TGA in September 2015 and accepted for evaluation.

Evaluator's overall conclusions on the Search Strategy

The proposed search strategy, including the selection criteria, was provided to the TGA for approval. Following some minor changes, a revised search strategy was approved by the TGA. The search strategy and selection criteria are appropriate for the proposed indication, although inclusion of publications that met all criteria except for that of '*an increased risk of developing breast cancer*', such as the Italian Prevention Study, may have provided additional safety information.

Evaluator's overall conclusions on the Search Results

Overall, the search results were satisfactory.

Excluded Studies

Titles, with or without abstracts, for all excluded publications were included. The abstracts of 1620 of the excluded publications were read by the evaluator. This did not identify publications mistakenly excluded. It is arguable that publications related to the Italian Prevention Study should have been included, even though it did not meet the strict inclusion criteria, given that it is included in the pivotal meta-analysis. However, given that it included women who had had a hysterectomy, regardless of risk of breast cancer and given that enrolment was ceased earlier than planned, due to low recruitment numbers, it would at most be considered supportive. It is also not clear as to why the health related quality of life publication based on the NSABP P1 trial[10] was excluded, although the follow-on publication (Day 2001) was included.

Included Studies

Of the included studies, Fisher 2005 may be better described as supportive rather than pivotal as the follow-up was largely unblinded. It is also arguable as to whether the HOT study should have been included (even as a secondary supportive study) given that the dose of tamoxifen used was 5 mg daily (not the 20 mg daily proposed for this indication) and given that women were recruited on the basis of being post-menopausal and prepared to take hormone replacement therapy (HRT) rather than having an increased risk of breast cancer (that is, this study did not meet the strict inclusion criteria). Fallowfield 2001, which presents the results of a subgroup of women from the Royal Marsden and IBIS-1 studies who prospectively completed surveys of psychological well-being, is more correctly described as an ancillary study than a meta-analysis.

See Clinical Questions Search Strategies and Results 1-4 in Attachment 2.

Dosage selection for the pivotal studies

A dose of tamoxifen 20 mg was used in all described risk reduction studies (except for the HOT study). No rationale for this dose was provided in the related publications. A duration of treatment of 5 years was used in 3 of the 4 main trials, with this apparently based on the duration of treatment in adjuvant trials (Vogel 2010). The Royal Marsden trial had a planned duration of treatment of 8 years. No rationale for this duration of treatment was described in the publications.

The sponsor proposes a maximum dose of oral tamoxifen 20 mg daily for 5 years for the proposed indication, on the basis of the dose and duration used in the larger risk reduction trials (IBIS-1 and NSABP P1)

[10] Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999;17:2659–69

The proposed dose of 20 mg daily is in keeping with the publications that showed efficacy in risk reduction of breast cancer in women at increased risk. The proposed duration of 5 years is in keeping with the key trials IBIS-1 and NSABP P1.

Publications included

The evaluator has reviewed each of the publications cited for safety and efficacy assessments in the dossier. A summary table is provided below (Table 1 in Attachment 2) with a description of the main trials, together with a listing of the publications based on each trial and their relationship to the main trials. Summaries and descriptions of the meta-analyses are also provided (Attachment 2 Section 17).

The key publication reporting each trial, and any publications reporting extended follow-up, are described in detail. Any other publications described as pivotal by the sponsor for either the safety or efficacy assessment are also described in detail. Publications included as supportive by the sponsor are described more briefly. A short description of the 'Italian Prevention Study' is also provided to provide context to the references to this study in the pivotal meta-analyses. This trial was not included in the dossier by the sponsor as the inclusion criteria did not match the indication.

Efficacy

Publications identified through the literature search in support of efficacy

For the indication of the primary prevention of breast cancer in women at increased risk of breast cancer

There were 20 identified publications, presenting results from 4 randomised, placebo-controlled trials (IBIS-1, NSABP P1, Royal Marsden), and 1 randomised, controlled trial comparing tamoxifen with raloxifene (STAR). The publications present overall results, long-term results and sub-group analyses from these trials. In addition, 3 meta-analyses were identified (Cuzick 2013, Nelson 2013, and Duffy 2002)

Summaries of these publications were provided by the sponsor in the Clinical Overview.

The evaluator has reviewed each of the publications cited for the efficacy assessment. A summary table is provided above in with a description of the main trials, together with a listing the publications based on each trial and their relationship to the main trials.

Pivotal Publications

Publications included as pivotal for the assessment of efficacy were: Cuzick 2013 (meta-analysis); Cuzick 2002, 2007 and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Powles 1998 and 2007 (results of the Royal Marsden trial); see Table 2 in Attachment 2.

Of the included 'pivotal' publications:

- The objective of the meta-analysis Cuzick 2013 was to assess the effectiveness of all SERMs in the reduction of breast cancer. It used individual participant data from nine prevention trials comparing four selective oestrogen receptor modulators (SERMs; tamoxifen, raloxifene, arzoxifene, and lasofoxifene) with placebo, or in one study with tamoxifen compared to raloxifene. Of the studies comparing tamoxifen to placebo, one study (the Italian Prevention study) did not have increased risk of breast cancer as one of the inclusion criteria.

- The second report of the NSABP P1 trial, Fisher 2005, may be better described as supportive rather than pivotal as the follow-up was open and affected by both potential bias and crossover from placebo to tamoxifen following unblinding of the NSABP P1 trial in 1998.

Of note is that the publication Iqbal 2012, a meta-analysis included for the safety assessment provides a discussion of the differences between the three main tamoxifen breast cancer risk reduction trials (IBIS-1, NSABP P1, and Royal Marsden), summarises the key results from each trial and provides a formal assessment of the risk of bias in each trial.

Evaluator's conclusions on clinical efficacy for the indication of the primary prevention of breast cancer in women at increased risk of breast cancer

The evaluator agrees with the sponsor that tamoxifen is efficacious in reducing the incidence of breast cancer in women aged more than 30 years who were at increased risk of breast cancer. The meta-analysis Nelson 2013 estimated that tamoxifen reduced the incidence of invasive breast cancer by 7 to 9 cases in 1000 women over 5 years compared with placebo. Cuzick 2015 estimates that the number needed to treat for 5 years to prevent one breast cancer in the next 20 years was 22 (95% CI 19–26)and the number needed to treat to prevent one invasive oestrogen receptor-positive breast cancer was 29 (95% CI 26–34).

The reduction in breast cancer incidence was mainly through the reduction in the incidence of ER-positive cancers. The meta-analysis Cuzick 2013 found that for the tamoxifen vs placebo trials included (Royal Marsden, NSABP P1, IBIS-1 and the Italian Prevention study), the reduction in the Hazard Ratio was 33% (p<0·0001) for all breast cancers and 44% (p<0·0001) for ER-positive breast cancer. A non-significant increase in ER-negative tumours was also described. The reduction in incidence persisted throughout the follow-up periods of the pivotal studies (for median of 13 and 16 years for those trials that remained blinded), suggesting that tamoxifen has not simply delayed the onset of breast cancers. It is unclear from currently available evidence as to whether menopausal status or the concurrent use of HRT may alter the effect of tamoxifen on the incidence of breast cancer.

The clinical evaluator is of the opinion that other measures of efficacy (mortality and quality of life) that were not discussed in the sponsor's Clinical Overview but were examined in the pivotal trials should also be included in the assessment of efficacy (see Clinical Question Efficacy 5 and 6 Attachment 2). The results for these outcome measures, as available, are described below.

Mortality

Each of the pivotal trials (IBIS-1, NSABP P1, and Royal Marsden) included breast cancer specific and overall mortality as a secondary outcome measures. The most recent publication for each trial (Cuzick 2015, Fisher 2005, and Powles 2007) reported no significant difference in overall mortality with tamoxifen compared to placebo; see Table 2 below.

Table 2: Mortality Results from NSABP P1, Royal Marsden, and IBIS-1 Trials

	NSABP P1		Royal Marsden		IBIS-1	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
	n=6466	n=6498	1238	1233	n=3573	n=3566

	NSABP P1		Royal Marsden		IBIS-1	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
	n=6466	n=6498	1238	1233	n=3573	n=3566
Deaths, all cause - number (%)	57 (0.9)	71 (1.1)	54 (4.4)	54 (4.4)	182 (5.1)	166 (4.7)
RR, OR (95% CI)	RR 0.81 (0.56-1.16)		NA		OR 1.1, (0.88-1.37)	
Deaths, breast cancer specific - number (%)	3 (0.05)	6 (0.09)	12 (1.0)	9 (0.7)	31 (0.9)	26 (0.7)
OR, (95% CI)	NA		NA		NA	

Table constructed from Table 3 Powles 2007, Table 7 Cuzick 2015 and text Fisher 2005. Note that after 1998, women in the placebo arm of the NSABP P1 trial could crossover to the tamoxifen arm

The pivotal meta-analysis (Cuzick 2013) commented that '*No trial was designed to look at mortality as an endpoint, and no effect of any SERM was reported for all causes of death*' and that '*No effect on breast cancer death was reported in the tamoxifen trials*'. The Nelson 2013 systematic review also found that tamoxifen did not reduce breast cancer specific mortality (RR 1.07, 95%CI 0.66-1.74) or all-cause mortality (RR 1.07, 95%CI 0.90-1.27).

Quality of Life

Quality of life was a secondary outcome measure in the NSABP P1 trial. This outcome was not reported in the main publications related to this trial. A publication of the analysis of the results for 11,064 women for the first 36 months of follow-up was separately reported in

> *Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659–69.*

This publication was not included by the sponsor (see Clinical Question Search Strategy and Results 3 Attachment 2). From the publically available abstract of this publication, no differences were found between placebo and tamoxifen groups using the quality of life measures of Center for Epidemiological Studies-Depression Scale (CES-D) and the Medical Outcomes Study 36-Item Short Form Health Status Survey (MOS SF-36); more women on tamoxifen reported problems of sexual functioning; and the mean number of symptoms reported using a symptom checklist was consistently higher in the tamoxifen group and was associated with vasomotor and gynaecologic symptoms.

Fallowfield 2001 describes an ancillary study of a convenience sample of 488 women enrolled in the Royal Marsden and IBIS-1 trials who completed a set of questionnaires regarding psychosocial and sexual well-being and a symptom checklist (by post) every 6 months for 5 years from commencement of their participation in the trial. This study found that preventative tamoxifen in women at increased risk of breast cancer was not associated with changes in psychological or sexual well-being, despite women in the tamoxifen group being more likely to report vasomotor symptoms (night sweats, hot flushes and cold sweats) and vaginal discharge.

Adherence to the Regimen

Efficacy of tamoxifen for the proposed indication will depend on whether outcome of the risk-benefit discussion between the prescriber and the individual woman indicates that prescription is appropriate and then on whether the woman takes tamoxifen as prescribed.

Available information would indicate that adherence to the treatment regimen (tamoxifen 20 mg daily for 5 or 8 years) was low, although this measure together with treatment discontinuations was poorly described in the pivotal trials. The information available is provided below:

- In the Royal Marsden trial, 35.5% of women did not complete the planned 8 years of treatment (25.8% of the tamoxifen group and 14.3% of the placebo group, P=0.002).
- The meta-analysis Nelson 2013 found that '*In NSABP P-1, 41% of participants took 100% of study medication and 79% took at least 76% of study medication at 36 months. Forgetting was the primary reason for nonadherence for 62% of women at 36 months* '(page 608). In Day 2001, it was reported that 3539 women in the NSABP P1 trial completed an 'Off therapy form' after discontinuing treatment with tamoxifen early and that '*The most frequent reasons for going off therapy were nonmedical in nature (1667 women [47.1%]), perceived toxic effects (921 women [26.0%]), and various protocol and non-protocol medical conditions (841 women [23.8%])'* (page 1620).
- A sub-group analysis of Finnish women participating in the IBIS-1 trial (N= 96, 45 were treated with tamoxifen and 51 with placebo) found that women in the tamoxifen group were significantly more likely to discontinue the study compared to the placebo group (20/45, 44% compared to 11/51, 22%, p=0.017). The most common reason for discontinuation in the tamoxifen group was vasomotor symptoms (10/20). The median time for discontinuation in the tamoxifen group was 15 months (range 2-60months) compared to 30 months (range 14-44) in the placebo group (Palva 2013).

Nelson 2013 also reviewed women's responses to the risk/benefit of tamoxifen and found that '*A study of women with elevated risk scores reported that 12% of women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided. Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining. However, 90% of women stated that they would take a medication with the same benefit as tamoxifen if it had no side effects, and one half would take a medication with the same side effects as tamoxifen if it could eliminate the chance of getting breast cancer'* (page 608).

From this it would appear that it would be common for women at increased risk of breast cancer to either decline, or fail to complete, a 5 year course of tamoxifen. This will reduce to potential for any efficacy benefits to be realised (see also Clinical Question Efficacy 7 Attachment 2). No analysis of the actual duration of tamoxifen therapy against efficacy in reduction of the incidence of breast cancer is presented in the publications provided.

Summary

Use of tamoxifen (20 mg daily for 5 years) has been associated with a clinically and statistically significant decrease in the incidence of invasive breast cancer (mainly through a reduction in the incidence of ER-positive cancer) in women at increased risk of breast cancer. Although tamoxifen treatment was not apparently associated with a decrease in psychosocial well-being during treatment, adherence to the planned regimen was low across the trials. The reduction in the incidence of invasive breast cancer did not translate to a reduction in either all-cause or breast-cancer specific mortality during follow-up of up to 20 years.

The incidence of invasive breast cancer observed in the tamoxifen arms of the pivotal trials is lower than that of the placebo arms but is not reduced to zero. Therefore, it may be more appropriate to use the terminology of 'primary risk reduction' rather than 'primary prevention' in the proposed indication. It would also be appropriate that the lack of demonstrated efficacy on mortality be included in the PI.

Safety

Studies providing evaluable safety data

The publications for the safety assessment include results from the same 4 randomised, placebo-controlled trials (IBIS-1, NSABP P1, Royal Marsden), and 1 randomised, controlled trial comparing tamoxifen with raloxifene (STAR) that were identified through the efficacy assessment. The Hormone Replacement Therapy Opposed by Low Dose Tamoxifen (HOT) study, a non-randomised trial (Imperato 2003) and 5 meta-analyses (Cuzick 2013, Braithwaite 2003, Iqbal 2012, Fallowfield 2001, Nelson 2013) were also included for the safety assessment

Summaries of these publications were provided by the sponsor in the Clinical Overview.

Fallowfield 2001 is more correctly described as an ancillary study to the IBIS-1 and Royal Marsden trials than as a meta-analysis – see description below

Pivotal Publications

Publications identified as pivotal by the sponsor for the assessment of safety were: Cuzick 2103 (meta-analysis); Cuzick 2002, 2007 and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Reis 2001; Land 2006; Vogel 2006 & 2010 (results of the STAR trial). See Table 5 in Attachment 2 for details.

Of the included 'pivotal' publications with the efficacy assessment:

- The objective of the meta-analysis Cuzick 2013 was to assess the effectiveness of all SERMs in the reduction of breast cancer. Not all of the results provided separate out those for participants receiving tamoxifen.
- Fisher 2005 may be better described as supportive rather than pivotal as the follow-up was largely open and affected by crossover following unblinding of the NSABP P1 trial in 1998.
- The STAR trial only included post-menopausal women (a subset of the proposed population) and included an active comparator arm (raloxifene). In Land 2006, the quality of life assessment was performed on a small sub-group, 1983 of the total cohort of 19747

Patient exposure

THE PBRER provides the following information:

The total worldwide exposure to Nolvadex for the period of 30 April 2013 to 29 April 2014 was calculated from the number of tablets delivered to wholesalers worldwide during the period. A daily dose of 20 mg has been assumed. The total worldwide exposure, for this PBRER reporting period, has been estimated by AstraZeneca to be 293,040 patient-years.

It has not been possible to estimate the total worldwide exposure since launch in 1973 to 29 April 2014 as the AstraZeneca legacy systems and documents containing early data are now not available. However, it has been possible to calculate exposure since the beginning of 2001 to 29 April 2014; patient exposure for this period has been estimated by AstraZeneca to be 5.9 million patient years.

Marketing approval(s): *Nolvadex 10 mg was first approved for marketing in the United Kingdom (UK) on 30 August 1973, Nolvadex 20 mg was first approved on 29 January 1982 and both are currently approved in over 60 countries including some European Union (EU) member states. Nolvadex 30 mg and 40 mg were subsequently approved in a small number of countries but most of these approvals are now withdrawn and the use of these tablets has*

ceased. These withdrawals have been motivated by commercial reasons, and are not related to any safety concerns.

Postmarketing experience

Information regarding post-marketing experience has been provided in the sponsor's Summary of Clinical Safety and in the Periodic Benefit-Risk Evaluation Report (PBRER) for the period 30 April 2013 to 29 April 2014. Of note is that tamoxifen for the indication of primary prevention of breast cancer in women at increased risk of breast cancer is only approved in the USA. Post-marketing experience is therefore largely limited to the use of tamoxifen in the treatment of breast cancer.

The appendix of the PBRER included in the dossier provides tabulated cumulative summaries of:

1. Case reports containing Serious Adverse Events (SAEs) from AstraZeneca-sponsored interventional clinical trials from the Development International Birth Date (DIBD) to the
2. Case reports of serious and non-serious adverse events from spontaneous sources from IBD to the PBRER data lock point (29 April 2014)

These tables have been summarised by the evaluator to include System Organ Class (SOC) and Preferred Terms (PT) for the most common events or events of special interest, where the evaluator has defined these as events identified as important risks or events that were reported in the pivotal publications. These tables have been included as Tables 8 and 9 (compiled from the PBER provided) in Attachment 2.

Overall, the cumulative listings are consistent with the Important Identified Risks in the PBRER and with the Precautions and Adverse Events as described in the PI. Serious adverse events described in the PBRER and current PI as associated with tamoxifen use that were not described in the publications presented in the dossier included: ischaemic cerebrovascular events; isolated reports of skin reactions such as erythema multiforme and Stevens-Johnson syndrome; uncommon reports of interstitial pneumonitis, liver injury (as described above under Important Identified Risks) and rare reports of optic neuropathy/neuritis, cutaneous lupus erythematosus, elevated triglycerides with pancreatitis. Fatigue, nausea and vomiting have been very commonly reported with tamoxifen use.

See Tables 8 and 9 in Attachment 2 for details of the Cumulative reports of adverse events from clinical studies (compiled from the PBRER)

Evaluator's conclusions on safety

The use of tamoxifen for risk reduction in women at increased risk of breast cancer is associated with both serious and non-serious adverse events.

Potentially life-threatening adverse events include venous thromboembolic events and uterine cancer:

- It was estimated in the Nelson 2013 meta-analysis that tamoxifen increased the risk for venous thromboembolic events (VTEs) by 4 to 7 events per 1000 women over 5 years. The risk of VTE with tamoxifen was higher in women aged 50 years or more compared to women aged less than 50 years. It was also found that factors such as recent surgery, immobility and lower limb fractures further increased the risk of VTE in women taking tamoxifen.
- It was estimated in the Nelson 2013 meta-analysis that tamoxifen increased risk for endometrial cancer by approximately 4 cases per 1000 women The risk of

endometrial cancer with tamoxifen was only increased in women aged 50 years or more; the incidence of endometrial cancer in women aged less than 50 years taking tamoxifen did not differ from the placebo group. The presence of a uterus also determined the risk of endometrial cancer.

Less serious adverse effects that were more common with tamoxifen included other gynaecological conditions and procedures, including hysterectomy and cataracts. Symptoms such as hot flushes, night sweats and vaginal discharge were very common in women taking tamoxifen. These symptoms, although not classified as serious, may affect a patient's quality of life and willingness to use or adhere to these medications.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of tamoxifen in the proposed usage are:

- Reduction in the incidence of potentially life-threatening invasive breast cancer in healthy women at increased risk of breast cancer

First round assessment of risks

The risks of tamoxifen in the proposed usage are:

- Increased risk of potentially life-threatening adverse events such as pulmonary embolism and uterine cancer
- Likely experience of the common side effects of fatigue, nausea and vomiting, hot flushes, night sweats, vaginal discharge and benign gynaecological conditions. These side effects are not typically classified as serious but may affect a woman's quality of life and willingness to continue use of tamoxifen
- Unclear risk of osteoporotic fractures in relation to tamoxifen use and menopausal status
- Tamoxifen should not be used in women who have a history of thromboembolic events (deep venous thrombosis and pulmonary embolus)

First round assessment of benefit-risk balance

The potential benefit of tamoxifen for the proposed usage is a reduction in the incidence of potentially life-threatening invasive breast cancer. Against this, are the potential life-threatening risks of endometrial cancer and thromboembolic disease and the discomfort and inconvenience of the common side effects of hot flushes, night sweats, vaginal discharge and benign gynaecological conditions.

Determining the benefit-risk balance of tamoxifen for the indication of the reduction of the risk of breast cancer in healthy women at increased risk of breast cancer is complex as the potential risks and benefits may vary considerably between individual women. The woman's personal risk of breast cancer will vary with age and other factors such as family history, parity and breast feeding. The risk of adverse events with tamoxifen will vary with the woman's age and menopausal status, whether the woman has a uterus and other factors.

Two of the publications provided in the dossier have attempted to address some of these complexities and provide an assessment of the risk-benefits. Fisher 2005 presented breast cancer cases prevented against VTE and endometrial cancer cases caused, according to age group, risk of breast cancer and race in the following graphs (Figure 2):

Figure 2: Benefits and risks associated with tamoxifen use for breast cancer risk reduction

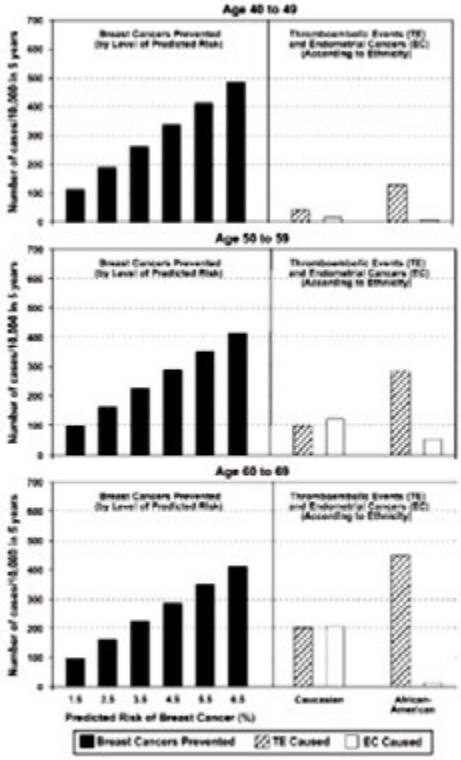


Fig. 4. Benefits and risks associated with tamoxifen use for breast cancer risk reduction. Numbers of breast cancers prevented by tamoxifen in cases per 10 000 women over 5 years by 10-year age group and by level of predicted risk (**left**). Numbers of thromboembolic events and endometrial cancers caused by tamoxifen in cases per 10 000 women over 5 years, by ethnicity (**right**).

Freedman 2011 used data from the NSABP P1 and STAR studies, together with surveys to determine background incidence rates, to develop a risk matrix for women with or without a uterus and according to the 5 year projected risk of breast cancer (see Table 9 in Attachment 2).

The woman's personal assessment of the risk and benefit, together with her own tolerance of the different risks must also be considered. Nelson 2013 reported a study of women with elevated risk for the development of breast cancer: 12% of these women selected tamoxifen for breast cancer risk reduction, 77% declined and 12% were undecided. Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining.

The judgement as to whether the use of 'preventative' tamoxifen is appropriate in a particular woman requires careful weighing up of these risks and benefits together with consideration of how risk-averse the woman is regarding her personal risk of breast cancer or adverse effects. It is therefore essential that this is a shared decision making process and that the individual woman is provided with the necessary information with which to make an informed decision. This would most appropriately be achieved through discussion with a specialist with knowledge and experience in the management of breast and familial cancer. If the planned 5 years of treatment is to be completed by a healthy woman, it is necessary that the woman engage in the decision-making process and understands the relevance to her personal situation. For women who choose to commence risk reduction therapy with tamoxifen, careful advice must also be given regarding the need for review if symptoms/signs of thromboembolic events develop or abnormal gynaecological symptoms develop. The information provided in the PI and Consumer Medicine Information (CMI) must form an integral part of both the decision-making process and monitoring during therapy.

The benefit-risk balance of tamoxifen for the proposed usage is favourable provided the recommendations made in regard to the PI and CMI below are agreed to.

First Round Recommendation Regarding Authorisation

The clinical evaluator recommends that tamoxifen be approved for the proposed usage, provided the suggestions made with regard to the PI and CMI are agreed to.

Approval of tamoxifen for this usage is consistent with the publically available recommendations of reputable groups such as the Australian federal government agency Cancer Australia, the national non-government organisation Cancer Council Australia, the professional body American Society of Clinical Oncology and the UK National Institute for Health and Care Excellence (NICE).

Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical evaluator's questions, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tamoxifen in the proposed usage are unchanged from those identified in the First round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of tamoxifen in the proposed usage are unchanged from those identified in the First round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of tamoxifen is favourable given the proposed usage, provided the changes recommended to the PI and CMI are adopted.

Second round recommendation regarding authorisation

The evaluator recommends that tamoxifen be approved for the proposed usage, provided the suggestions made with regard to the PI and CMI are agreed to.

VI. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application. See *Specific conditions of registration applying to these goods* below.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Paediatric data

Appropriately, the submission did not include paediatric studies.

Efficacy

The key endpoint is reduction in the risk of invasive breast cancer and consistent with the mechanism of action, a reduction in risk of invasive ER-positive but not ER-negative breast cancer has been demonstrated; see Table 3 below. It would be very unlikely that studies such as this would demonstrate a reduction in mortality, especially as the trials participants have been identified as at an increased risk and they should be under active monitoring. This would be expected to result in early detection of any cancers in both the placebo and tamoxifen arms. This is before the consideration of many confounding effects of the subsequent treatment modalities, one of which would be endocrine therapy in the ER-positive subgroup.

Table 3: Summary of Efficacy Results from the Primary Risk Reduction Trials

Risk factor	Cuzick meta- analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,19 2 Events	Placeb n=14,214 Events	Tamox n=3579 Events	Placeb n=3575 Events	Tamox n=6597 Events	Placeb n=6610 Events	Tamox n=1238 Events	Placeb n=1233 Events
	HR (95% CI)		HR (95% CI)		RR (95% CI)		HR (95% CI)	
All breast cancer	431	634	251	350	205	343	96	113
	0.67 (0.59-0.76)		0.71 (0.60-0.83)		NR		NS	
Invasive breast cancer	NR		214	289	145	250	38 [e]	56 [e]
			0.73 (0.61-0.87)		0.57 (0.46-0.70)		0.67 (0.44-1.01)[e]	
Non-invasive cancers	77	112	35	53	60	93	NR	
	0.72 (0.57-0.92)		0.65 (0.43-1.00)		0.63 (0.45-0.89)			
Oestrogen receptor-positive cancers	219	396	160	238	70	182	53	86
	0.56 (0.47-0.67)		0.66 (0.54-0.81)		0.38 (0.28-0.50)		0.61 (0.43-0.86)	
Oestrogen receptor-	116	103	50	47	56	42	24	17

Risk factor	Cuzick meta- analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,19 2 Events	Placeb n=14,214 Events	Tamox n=3579 Events	Placeb n=3575 Events	Tamox n=6597 Events	Placeb n=6610 Events	Tamox n=1238 Events	Placeb n=1233 Events
	HR (95% CI)		HR (95% CI)		RR (95% CI)		HR (95% CI)	
negative cancers	NS		NS		NS		NS	

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = not significant, NR = not reported, placeb = placebo, RR = risk ratio, tamox = tamoxifen.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Royal Marsden primary risk reduction trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years

[e] Results shown for posttreatment period only. During treatment, invasive breast cancer incidence was not significantly different between the tamoxifen and placebo groups.

Of note, the non-significant reduction in invasive breast cancer risk overall in the Royal Marsden study is likely to be due to the small numbers in this trial, as well as the women being recruited perhaps not being as 'high risk' as the other studies. In the presence of a negative overall finding, subgroup analyses (especially where not prespecified) should be interpreted with caution, and considered exploratory. The finding of an effect in the ER-positive subgroup supports the findings in the other studies. However, the inclusion in the PI of a statement regarding there being no negative effect of hormone replacement therapy on the reduction in breast cancer rates by tamoxifen should be removed as this study was not powered to examine this and many patients commenced HRT at an unspecified time after commencing the study.

Similarly, subgroup analyses reported in the PI where the studies were insufficiently powered should be removed; for example the IBIS and Royal Marsden studies with regard to postmenopausal versus premenopausal status. The Delegate suggests that the only trial powered adequately was the NSABP P1 study and therefore only that should be reported in the PI.

The women in the Royal Marsden trial should be considered as having an 'increased' rather than 'high' risk. Some of the criteria for recruitment do not fall into the category considered 'high' risk.

Safety data

The adverse effects of tamoxifen are well known and in these studies no new signals emerged.

However, communication of these risks in the PI and CMI to enable informed consent is important particularly as the use in the preventative setting the benefit-risk considerations differ from those where there is metastatic disease or use in the adjuvant setting. Notably, both of these uses have demonstration of improvement in survival to support the usage.

Thus the remainder of this overview was aimed at ensuring the PI reflects in a clear way, the potential benefits and risks. This includes addressing the issues that remained outstanding following the Second round evaluation as supplied by the sponsor on 14 February 2016.

Clinical evaluator's recommendation

The clinical Evaluator recommends that tamoxifen be approved for the proposed usage, provided the suggestions made with regard to the PI and CMI are agreed to.

Risk management plan

No RMP was submitted for this application. It is considered that the PI and CMI would adequately address risk management issues. However, routine pharmacovigilance is required.

Risk-benefit analysis

Summary of issues

This literature based submission cites large, randomised controlled trials examining the effect on breast cancer incidence in women at increased risk of breast cancer. There is a reduction in the risk of oestrogen receptor-positive breast cancer but no oestrogen receptor-negative invasive breast cancer which is consistent with the mechanism of action.

Proposed action

The Delegate considers the following indication can be approved subject to the modification of the PI and CMI as Nolvadex is indicated for the primary reduction of breast cancer risk in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).

Conditions of registration

The following are proposed as conditions of registration:

1. Notwithstanding that the TGA has granted your application a waiver from the need to submit a Risk Management Plan (RMP); it remains a requirement that Routine Pharmacovigilance of this therapeutic good must be undertaken. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

   Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's *Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report* (Rev 1), Part VII.B. *Structures and processes*. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

   Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

You are reminded that sections 29A and 29AA of the *Therapeutic Goods Act 1989* provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

1. information that contradicts information already given by the person under this Act;
2. information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
3. information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
4. Information that indicates that the quality, safety or efficacy of the goods is unacceptable.

Response from Sponsor

On 21 January 2016, the sponsor received the final Clinical Evaluation Report from the TGA regarding the application '*Tamoxifen for the primary prevention of breast cancer in women at increased risk of breast cancer'* (submission number PM-2015-02360-1-4). The sponsor notes the clinical evaluator has confirmed that many of the points that were raised during the first round of evaluation and consolidated questions have been satisfactorily addressed by sponsor in their response to the consolidated request for further information. The sponsor also provided a response to the remaining points of difference, that is, the proposed amendments to the PI and CMI. Except for the discussion regarding the proposed indications (see below) the details of these questions and answers are beyond the scope of this AusPAR.

Indications section

Evaluator's comments

The evaluator remains of the opinion that the proposed indication should include the recommendation that:

> *'Treatment should be initiated by a specialist with expertise in managing breast cancer or familial cancer.'*

The evaluator's reason for the continued recommendation that a '*specialist with expertise in managing breast cancer or familial cancer*' should initiate treatment is due to the complexity of the risk-benefit assessment that must be made and ensuing discussion with the patient, to enable fully informed decision making by the patient.

The evaluator goes on to make reference to TGA guidance on the content of a PI and also refers to current clinical guidelines to support their argument for the insertion of the required statement.

The evaluator also notes the reference cited by the sponsor (Phillips et al 2015) documents existing barriers in Australia to breast cancer risk assessment and management by general practitioners (GPs) and '*identified several key issues that would need to be addressed to facilitate the transition to routine assessment and management of breast cancer risk in primary care*'.

Sponsor's response

The clinical evaluator makes an important point that an appropriate assessment of breast cancer risk is essential before prescribing tamoxifen for primary risk reduction. This is clearly stated in the Dosage and Administration section of the PI: '*An assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer risk is essential*'. However, the sponsor remains of the view that it is not appropriate or necessary to include a statement in the PI directing who should initiate treatment for the following reasons:

- The sponsor's position is that the draft PI as proposed satisfactorily fulfils each of the requirements set out in ARGPM Guidance 8. Guidance 8 does not require a PI to define exactly who should prescribe a product and, furthermore, it is the sponsor's view that the PI is not the place for such direction to be given.
- The sponsor maintains that clinical treatment guidelines are the most appropriate place for guidance as to who patients should be assessed and treated. The clinical evaluator tacitly acknowledges the value of these resources for this purpose by making reference to them in clarifying their position. These guidelines are continually updated to reflect changes in medical practice. Currently, these guidelines suggest that a referral to a specialist should be considered for women at moderate or high risk, but this is not mandated (that is, a general practitioner [GP] can currently choose to manage these women or refer them to a specialist). If these guidelines are amended in the future to recommend, for example, that breast cancer assessment and management be conducted by GPs, a definitive statement such as the one proposed by the evaluator will once again put the tamoxifen PI (including the multiple generic versions) unnecessarily out of step with clinical practice.
- Restricting the prescriber to being a 'specialist' will also likely limit the number of women who are able to use tamoxifen for primary risk reduction. Specialists do not have the capacity to meet and evaluate all women who are potentially eligible for tamoxifen treatment; if the PI mandates initiation of treatment by a specialist, women at moderate risk of developing breast cancer will not be able access treatment.
- The study conducted by Phillips et al. (Phillips et al. 2015) was a needs evaluation designed to identify key areas where GPs needed support in assessing breast cancer risk and managing women at increased risk. The study was conducted because '*To capitalise on advances in breast cancer prevention, all women would need to have their breast cancer risk formally assessed. With ~85% of Australians attending primary care clinics at least once a year, primary care is an opportune location for formal breast cancer risk assessment and management*.' Studies like this show that the medical community have already identified primary care as the most logical place to assess and manage breast cancer risk and they are committed to providing GPs with the support they need to do this.

Advisory Committee Considerations

The submission was not referred to the Advisory Committee on Prescription Medicines (ACPM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nolvadex and Nolvadex-D containing tamoxifen as citrate at 10 mg and 20 mg respectively, for the new indication:

Nolvadex/Nolvadex-D is indicated for the primary reduction of breast cancer risk in women either of moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).

Specific conditions of registration applying to these goods

Notwithstanding that the TGA has granted [this] application a waiver from the need to submit a Risk Management Plan (RMP), it remains a requirement that Routine Pharmacovigilance of this therapeutic good must be undertaken. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module Un-Periodic Safety Update Report (Rev I), Part VII. B. Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

You are reminded that sections 29A and 29AA of the *Therapeutic Goods Act 1989* provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

1. information that contradicts information already given by the person under this Act;
2. information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
3. information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
4. Information that indicates that the quality, safety or efficacy of the goods is unacceptable.

Attachment 1. Product Information

The PI for Nolvadex/Nolvadex-D approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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