

**6.09 TAMOXIFEN  
20 mg tablets,  
Novaldex-D®, AstraZeneca.**

**1 Purpose of Application**

1.1 Restricted Benefit listing for tamoxifen for the primary prevention of breast cancer in women at increased risk of breast cancer.

**2 Requested listing**

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. The Pre-PBAC Response accepted the proposed wording.

| Name, Restriction,<br>Manner of administration and form | Max.<br>Qty | №.of<br>Rpts<br>Units | Proprietary Name and Manufacturer |             |
|---|-------------|-----------------------|-----------------------------------|-------------|
| <b>FOR 12-MONTH SUPPLY:</b>                             |             |                       |                                   |             |
| TAMOXIFEN<br>20 mg tablet, 30                           | 60          | 5                     | Novaldex-D                        | AstraZeneca |
| <b><u>OR</u> FOR 6 MONTH SUPPLY:</b>                    |             |                       |                                   |             |
| TAMOXIFEN<br>20 mg tablet, 30                           | 30          | 5                     | Novaldex-D                        | AstraZeneca |

|                             |  |
|-----------------------------|--|
| Category / Program          | GENERAL – General Schedule (Code GE)   |
| Prescriber type:            | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives  |
| Condition:                  | <del>Primary prevention in women with moderate or high risk of developing breast cancer</del><br><del>Primary prevention of breast cancer</del> <i>Reduction of breast cancer risk</i>   |
| Treatment phase:            | <del>Initial</del>   |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined |

Public Summary Document – March 2016 PBAC Meeting

|                                    |  |
|------------------------------------|--|
| <b>Clinical criteria:</b>          | <p>Patient must have a moderate or high risk of developing breast cancer.</p> <p>AND</p> <p>The treatment must not exceed a dose of <del>The dose must not exceed</del> 20 mg per day.</p> <p>AND</p> <p>The treatment must not exceed a lifetime maximum of <del>The duration of prophylaxis must not exceed a lifetime total of</del> 5 years for this condition <del>the primary prevention of breast cancer.</del></p>   |
| <b>Administrative Advice</b>       | <p>A moderate risk of developing breast cancer is if the lifetime breast cancer risk is 1.5 to 3 times the population average. A high risk of developing breast cancer is if the lifetime breast cancer risk is more than 3 times the population average. A woman is considered at moderately increased risk of developing breast cancer if her lifetime breast cancer risk is 1.5 to 3 times the population average. A woman is considered at high risk if her lifetime breast cancer risk is more than 3 times the population average.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> |
| <b>Category / Program</b>          | GENERAL – General Schedule (Code GE)   |
| <b>Prescriber type:</b>            | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives  |
| <b>Condition:</b>                  | Primary prevention in women with moderate or high risk of developing breast cancer   |
| <b>Treatment phase:</b>            | Continuing treatment   |
| <b>Restriction Level / Method:</b> | <input checked="" type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required – In Writing<br><input type="checkbox"/> Authority Required – Telephone<br><input type="checkbox"/> Authority Required – Emergency<br><input type="checkbox"/> Authority Required – Electronic<br><input type="checkbox"/> Streamlined   |
| <b>Clinical criteria:</b>          | <p>Must have previously received PBS subsidised prophylaxis with tamoxifen for this indication.</p> <p>AND</p> <p>The dose must not exceed 20mg per day.</p> <p>AND</p> <p>The duration of prophylaxis must not exceed a lifetime total of 5 years for the primary prevention of breast cancer.</p>  |

2.2 The PSCR (p1) stated that based on the proposed TGA indication (see ‘Background’ section below), the revised requested PBS indication for this listing is for: “Reduction of breast cancer risk”. The Secretariat has made this amendment to the proposed restriction above.

2.3 The economic analysis and financial forecasts are based on the dispensed price for the alternative listing (6-months’ supply) rather than the requested listing (12-month supply).

- 2.4 The submission did not substantiate the request for listing of tamoxifen for “moderate to high risk women” versus “high risk women only”. The economic evaluation was performed for the moderate to high risk group and the high risk group, but not for the moderate risk group separately. Model outcomes were not compared for the high risk group versus the moderate to high risk group. The Pre-Sub-Committee Response (PSCR, p1) stated that the bulk of the comprehensive body of clinical evidence included in the Cuzick meta-analysis is in the moderate risk population. From the clinical data, the PSCR states that women at moderate risk derive the same relative risk reduction as those at high risk and represent the group with the greatest clinical need as they have no alternative risk reducing options available. Given that the vast majority of women who would benefit from tamoxifen treatment are at moderate risk of breast cancer, the PSCR argued it would be inequitable to deny these patients access to tamoxifen, and doing so would substantially restrict the potential for tamoxifen to reduce breast cancer incidence in Australia. While the ESC agreed that the same relative risk reduction is observed, the absolute risk is substantially less. The Pre-PBAC Response (p1) added that, ‘the greatest absolute number of breast cancers avoided will occur in the moderate risk group due to the population size.’ The PBAC noted that following the same logic, the greatest amount of overtreatment and toxicity will occur in the moderate risk group.
- 2.5 The submission provided a cost-utility analysis comparing “tamoxifen + watchful waiting” with “watchful waiting”.
- 2.6 This submission requested a listing specifically for Nolvadex-D® branded tamoxifen for the primary prevention of breast cancer, since the sponsors of the various generic brands of tamoxifen declined to participate in the registration and reimbursement process.
- 2.7 DUSC considered that a “Restricted Benefit” listing like the current PBS listing of tamoxifen or the treatment of hormone-dependent breast cancer would be appropriate.
- 2.8 DUSC considered that an arrangement allowing nurse practitioners to prescribe continuing therapy may be appropriate given the five year treatment period.
- 2.9 The submission proposed a maximum quantity of 60 tablets (2-months’ supply per script) and an alternative of 30 tablets per script. In case of 60 tablets per script, patients would only have to pay a co-payment once every 2 months instead of once every month. Furthermore, the maximum quantity of 60 tablets would allow a total of 12-months’ supply of tamoxifen which the submission stated would align with the annual clinical review for watchful waiting. The submission suggested that the standard 6-month supply could result in poor compliance should these women fail to visit their GP for a repeat prescription. However, a 6-month period may allow for closer monitoring of possible side effects.
- 2.10 DUSC considered that patients taking tamoxifen for the prevention of breast cancer are likely to be highly motivated and seek regular review. However, DUSC also considered that as this is the first medicine to be listed for prevention of cancer that it may be more appropriate for the original prescription with repeats to provide 6-months’ treatment as is standard for most PBS listed medicines. DUSC considered

that more frequent review may assist in detection and management of adverse events and encourage compliance.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **3 Background**

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available. The TGA Delegate's Overview stated that the proposed TGA indication for tamoxifen is: "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)".
- 3.2 Tamoxifen is currently available on the PBS for the treatment of hormone-dependent breast cancer.

### **4 Clinical place for the proposed therapy**

- 4.1 The submission proposed PBS listing for tamoxifen for the primary prevention of breast cancer in women with moderate to high risk of developing breast cancer. A woman was considered at moderately increased risk of developing breast cancer if her lifetime breast cancer risk is 1.5 to 3 times the population average. A woman was considered at high risk if her lifetime breast cancer risk is more than 3 times the population average.
- 4.2 The proposed place of tamoxifen is in primary prevention of breast cancer, where a patient can receive 5 years of PBS-subsidised treatment.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **5 Comparator**

- 5.1 The submission nominated "watchful waiting" as the main comparator. This is the appropriate comparator for moderate risk women and the majority of high risk women. Preventive surgery may be the appropriate comparator for a small proportion of high risk women. Preventive surgery as a comparator for high risk women was discussed at the September 2013 stakeholder meeting for tamoxifen in primary prevention of breast cancer. The PSCR (p1) stated 'The uptake of preventative surgery is very low in women at high risk of breast cancer; according to Collins 2013 (Med J Aust; 199 (10): 680-683) and a survey of 100 clinicians conducted for the submission, fewer than 1 in 5 high risk women elect to undergo bilateral mastectomy in Australian clinical practice.' The ESC agreed with the sponsor that watchful waiting is the appropriate comparator in high risk women.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 6 Consideration of the evidence

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the comments from the Breast Cancer Network Australia (BCNA). The comments described how “the use of tamoxifen for the reduction of breast cancer risk provides an important alternative option to surgery including removal of breasts and sometime ovaries, the latter being unacceptable to younger women who may wish to have a family.” The PBAC noted that the BCNA referred to research, which found that three per cent of women at moderate or high risk of breast cancer used tamoxifen to reduce their risk (Collins IM, Milne RL, Weideman P, McLachlan SA, Friedlander ML, kConFab Investigators, Hopper JL, Phillips KA. Preventing breast and ovarian cancer in high-risk BRCA1 and BRCA2 mutation carriers. *Med J Aust* 2013; 199 (10): 680-683). While supporting the clinical evidence provided in the submission, the PBAC noted that this study involved a clinician-driven sample, and likely overestimates wider usage.

6.3 The PBAC noted the advice received from the Medical Oncology Group of Australia (MOGA) supporting the PBS listing of tamoxifen for the prevention of breast cancer.

### ***Clinical trials***

6.4 The submission was based on a meta-analysis of four head-to-head trials comparing tamoxifen to placebo (n=28,444).

6.5 Details of the trials presented in the submission are provided in the table.

Table 1: Trials and associated reports presented in the submission

| Trial ID   | Protocol title/ Publication title   | Publication citation   |
|--|---|--|
| <b>Direct randomised trials</b>                  |   |  |
| IBIS-I   | Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, Hamed A, Howell A, Powles T. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial.<br>Cuzick J, Forbes J, Sestak I, Cawthorn S, Hamed A, Holli K, Howell A. Long-term results of tamoxifen prophylaxis for breast cancer – 96-month follow-up of the randomized IBIS-I trial.   | <i>Lancet</i> 2002; 360 (9336):817-824<br><br><i>Journal of the National Cancer Institute</i> 2007; 99 (4):272-282                                     |
| NSABP-1  | Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.<br>Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Carolyn D. Runowicz CD, James JM, Fordand LG, Wolmark N. Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. | <i>Journal of the National Cancer Institute</i> 1998; 90 (18):1371-1388<br><br><i>Journal of the National Cancer Institute</i> 2005; 97 (22):1652-1662 |
| Marsden  | Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J, Davey J. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial.<br>Powles T, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial.   | <i>Lancet</i> 1998; 352 (9122):98-101<br><br><i>Journal of the National Cancer Institute</i> 2007; 99 (4):283-290                                      |
| Italian  | Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, Boyle P. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women.<br>Veronesi U, Maisonneuve P, Rostmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Oliviero P, Lovison F, Gucciardo G, Rosselli del Turco M, Muraca MG, Pizzichetta MA, Conforti S, Decensi A. Tamoxifen for the prevention of breast cancer: late results of the Italian randomised tamoxifen prevention trial among women with hysterectomy           | <i>Lancet</i> 1998; 352 (9122):93-97<br><br><i>Journal of the National Cancer Institute</i> 2007; 99 (9):727-737                                       |
| <b>Meta-analyses of direct randomised trials</b> |   |  |
| Cuzick   | Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL.<br>Selective oestrogen receptor modulators in prevention of breast cancer: An updated meta-analysis of individual participant data.   | <i>Lancet</i> 2013; 381 (9880):1827-1834   |

Source: Tables B.2-2, B.2-3 and B.2-6 pp19, 20 and 25 of the submission.

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

| Trial                        | N      | Design / median FU                             | Risk of bias | Patient population                    | Primary outcome              | Use in modelled evaluation  |
|------------------------------|--------|--|--------------|---------------------------------------|------------------------------|-----------------------------|
| <b>Tamoxifen vs. placebo</b> |        |  |              |                                       |                              |                             |
| IBIS-I                       | 7,109  | R, DB, MC<br>8.0 year                          | Low          | High risk of BC, family history of BC | BC incidence                 | Not used                    |
| NSABP-1                      | 13,205 | R, DB, MC<br>4.8 year                          | Low          | >2x relative risk of BC               | BC incidence                 | Not used                    |
| Marsden                      | 2,471  | R, DB<br>14.3 years                            | Low          | >1.6% 5 year risk of BC               | BC incidence                 | Not used                    |
| Italian                      | 5,408  | R, DB, MC<br>11.6 years                        | Low          | Women with hysterectomy               | BC incidence<br>BC mortality | Not used                    |
| Meta-analysis Cuzick         | 28,444 | Included IBIS-I, NSABP-1, Marsden and Italian. |              |                                       | BC incidence                 | ER+ breast cancer incidence |

BC=breast cancer; DB=double blind; FU=follow-up; MC=multi-centre; R=randomised.  
Source: compiled during the evaluation

### **Comparative effectiveness**

6.7 The meta-analysis of clinical trials showed a significantly reduced incidence of breast cancer with the use of tamoxifen in moderate to high risk women (see Table 3). There was substantial heterogeneity between trials in the size of the effect, possibly due to differences in baseline breast cancer risk. A reduction in mortality has not been shown in any of the trials or the meta-analysis (see Table 4).

Table 3: Results of breast cancer incidence (year 0-10) across the direct randomised trials

| Trial ID                              | Tamoxifen<br>n with event/N<br>(%) | Placebo<br>n with event/N<br>(%) | Difference<br>between groups<br>(95% CI) | P-value  | NNT/NNH   |
|---------------------------------------|------------------------------------|----------------------------------|--|----------|---|
| <b>All breast cancer</b>              |                                    |                                  |  |          |   |
| IBIS-I                                | 143/3,573 (4.0)                    | 198/3,566 (5.6)                  | HR 0.72 (0.58, 0.90)                     | NR       | NNT: 65   |
| NSABP-1                               | 130/6,681 (1.9)                    | 248/6,707 (3.7)                  | HR 0.52 (0.42, 0.64)                     | NR       | NNT: 57   |
| Marsden                               | 96/1,238 (7.8)                     | 114/1,233 (9.2)                  | HR 0.87 (0.63, 1.21)                     | NR       | NNT: 67   |
| Italian                               | 62/2,700 (2.3)                     | 74/2,708 (2.7)                   | HR 0.83 (0.58, 1.19)                     | NR       | NNT: 229  |
| Meta-analysis<br>Cuzick               | 431/14,192 (3.0)                   | 634/14,214 (4.5)                 | HR 0.67 (0.59, 0.76)                     | <0.0001  | NNT (prevent BC): 70<br>NNH (cause endometrial cancer): 318<br>NNH (cause DVT/thrombotic event): 263<br>NNH (cause cataract): 142 |
| Chi-square for heterogeneity: P=0.02. |                                    |                                  |  |          |   |
| <b>ER+ breast cancer</b>              |                                    |                                  |  |          |   |
| IBIS-I                                | 88/3,573 (2.5)                     | 131/3,566 (3.7)                  | HR 0.69 (0.52, 0.90)                     | NR       | NNT: 83   |
| NSABP-1                               | 44/6,681 (0.7)                     | 134/6,707 (2.0)                  | HR 0.33 (0.23, 0.46)                     | NR       | NNT: 75   |
| Marsden                               | 51/1,238 (4.1)                     | 83/1,233 (6.7)                   | HR 0.66 (0.44, 0.99)                     | NR       | NNT: 38   |
| Italian                               | 36/2,700 (1.3)                     | 48/2,708 (1.8)                   | HR 0.73 (0.45, 1.17)                     | NR       | NNT: 228  |
| Meta-analysis<br>Cuzick               | 219/14,192 (1.5)                   | 396/14,214 (2.8)                 | HR 0.56 (0.47, 0.67)                     | <0.00001 | NNT (prevent ER+BC): 80   |
| Chi-square for heterogeneity: P=0.03. |                                    |                                  |  |          |   |

Abbreviations: BC = breast cancer; ER+ = estrogen receptor positive; DVT = deep vein thrombosis; NNH = number needed to harm; NR = not reported; NNT = number needed to treat.

Source: Tables B.6-1, p44 and B.6-2, p45 of the submission.

Table 4: Incidence of all-cause mortality in the randomised trials

| Trial                | Tamoxifen<br>n/N (%) | Placebo<br>n/N (%) | Difference between<br>groups (95% CI) | P-value |
|----------------------|----------------------|--------------------|---------------------------------------|---------|
| IBIS-I               | 65/3573 (1.8)        | 55/3566 (1.5)      | RR 1.18 (0.81, 1.73)                  | NR      |
| NSABP-1              | 59/6681 (0.9)        | 71/6707 (1.1)      | RR 1.10 (0.85, 1.43)                  | NR      |
| Marsden              | 54/1238 (4.4)        | 54/1233 (4.4)      | HR 0.99 (0.68, 1.44)                  | 0.95    |
| Italian              | 36/2700 (1.3)        | 38/2708 (1.4)      | RR 0.95 (0.60, 1.49)                  | NR      |
| Meta-analysis Cuzick | 214/14,192 (1.5)     | 218/14,214 (1.5)   | RR 0.98 (0.82, 1.19)                  | 0.86    |

Abbreviations: HR = hazard ratio; NR = not reported; RR = relative risk.

Source: Table B.6-4, p48 of the submission.

### Comparative harms

6.8 The meta-analysis by Cuzick et al. (2013) showed the incidence of endometrial cancer (HR 2.18, 95% CI 1.39-3.42), thromboembolic events (OR 1.60, 95% CI 1.21-2.12) and cataract (OR 1.10, 95% CI 1.01-1.21) was statistically significantly increased with tamoxifen for the prevention of breast cancer. Few adverse events occurred after therapy ceased. All-cause mortality was not statistically significantly different between the groups in any of the trials or the meta-analysis (see Table 4).

### Benefits/harms

6.9 A summary of the comparative benefits and harms for tamoxifen versus placebo is presented in the table below.

Table 5: Summary of comparative benefits and harms for tamoxifen and placebo

| Trial                            | Tamoxifen  | Placebo    | HR<br>(95% CI)          | Event rate/100 patients in<br>years 0-10 |         | RD<br>(95% CI)                |
|----------------------------------|------------|------------|-------------------------|--|---------|-------------------------------|
|                                  |            |            |                         | Tamoxifen                                | Placebo |                               |
| <b>Benefits</b>                  |            |            |                         |  |         |                               |
| <b>All breast cancer</b>         |            |            |                         |  |         |                               |
| Meta-analysis<br>Cuzick          | 431/14,192 | 634/14,214 | HR 0.67<br>(0.59, 0.76) | 3.04                                     | 4.46    | 0.014<br>(0.010,<br>0.019)    |
| <b>ER+ breast cancer</b>         |            |            |                         |  |         |                               |
| Meta-analysis<br>Cuzick          | 219/14,192 | 396/14,214 | HR 0.56<br>(0.47, 0.67) | 1.54                                     | 2.79    | 0.012<br>(0.009,<br>0.016)    |
| <b>Harms</b>                     |            |            |                         |  |         |                               |
|                                  | Tamoxifen  | Placebo    | HR / OR<br>(95% CI)     | Event rate/100 patients in<br>years 0-10 |         | RD<br>(95% CI)                |
|                                  |            |            |                         | Tamoxifen                                | Placebo |                               |
| <b>Endometrial cancer</b>        |            |            |                         |  |         |                               |
| Meta-analysis<br>Cuzick          | 67/11,492  | 31/11,506  | HR 2.18<br>(1.39, 3.42) | 0.58                                     | 0.27    | -0.003<br>(-0.005,-<br>0.002) |
| <b>DVT or pulmonary embolism</b> |            |            |                         |  |         |                               |
| Meta-analysis<br>Cuzick          | 131/12,954 | 82/12,981  | OR 1.60<br>(1.21, 2.12) | 1.01                                     | 0.63    | -0.004<br>(-0.006,-<br>0.002) |
| <b>Cataracts</b>                 |            |            |                         |  |         |                               |
| Meta-analysis<br>Cuzick          | 654/10,254 | 583/10,273 | OR 1.10<br>(1.01, 1.21) | 6.38                                     | 5.68    | -0.007<br>(-0.014,-<br>0.001) |

Abbreviations: HR = hazard ratio; OR = odds ratio; RD = risk difference.

Source: Tables B.6-2, p45, B.6-5, p49, B.6-7, p51 and B.6-9, p54 of the submission.

6.10 On the basis of direct comparison evidence presented by the submission, for every 1,000 patients treated with tamoxifen in comparison to placebo, over a 10 year period:

- approximately 14 fewer patients would develop breast cancer.
- approximately 3 additional patients would develop endometrial cancer.
- approximately 4 additional patients would develop DVT or pulmonary embolism.

- approximately 7 additional patients would develop cataract.
- approximately the same number of patients would die.
- approximately the same number of patients would die of breast cancer.

### **Clinical claim**

- 6.11 The submission described tamoxifen as clinically superior to placebo in reducing the incidence of breast cancer and inferior to placebo in terms of comparative safety. Clinical superiority was adequately supported in terms of the incidence of breast cancer but not in terms of survival.
- Based on the meta-analysis by Cuzick et al. (2013), tamoxifen reduces the incidence of invasive ER+ breast cancer in women at elevated risk. Tamoxifen did not significantly reduce breast cancer mortality or all-cause mortality.
  - Tamoxifen is inferior in terms of safety due to an increased incidence of endometrial cancer, thromboembolic events and cataracts.
- 6.12 The PSCR (p1) reiterated benefits of reducing the incidence of breast cancer following treatment with tamoxifen. The ESC noted the comment in *Lancet Oncology* (2015, 16:7-9) that stated 'The discordance between tamoxifen's effects on breast cancer incidence and outcome noted in the IBIS-I [clinical trial] update could merely represent the effects of chance alone, or alternatively might indicate that tamoxifen mainly decreases the incidence of cancers with a very favourable prognosis, increases cancers with unfavourable outcomes, or both'. Estrogen receptor positive (ER+) breast cancer survival post-tamoxifen may differ from overall breast cancer survival. The ESC noted that while survival may differ between ER+ and overall breast cancer survival, the ER status of the tumour would not be known in advance. The Pre-PBAC Response (p1) argued that the sponsor 'believes the speculation on a potential increase in breast cancer mortality, based on a letter of comment [in *Lancet Oncology*], is inappropriate and not supported by the comprehensive body of clinical evidence provided in the Cuzick meta-analysis (based on four randomised trials).' The PBAC noted that it is equally inappropriate for the sponsor to model a reduction in breast cancer mortality beyond year 10.
- 6.13 The PBAC considered that the claim of superior comparative effectiveness in terms of reducing the incidence of breast cancer was reasonable. The PBAC considered that a claim of clinical superiority in terms of survival was not adequately supported by the data.
- 6.14 The PBAC considered that the claim of inferior comparative safety was reasonable.

### **Economic analysis**

- 6.15 The submission presented a modelled evaluation.

Table 6: Summary of the model

| Component                        | Summary  |
|----------------------------------|--|
| Time horizon                     | Lifetime (70 years) in the model base-case versus 10 years in the meta-analysis.   |
| Outcomes                         | Costs per QALY gained.   |
| Methods used to generate results | A state transition model was used to generate the results by modelling participants based primarily on the Cuzick 2013 meta-analysis.  |
| Health states                    | <ul style="list-style-type: none"> <li>- Moderate/high risk of breast cancer.</li> <li>- ER+ breast cancer.</li> <li>- Other breast cancer.</li> <li>- Death (absorbing state).</li> <li>- Adverse events (transient states).</li> </ul>   |
| Cycle length                     | 1 year.  |
| Transition probabilities         | <p>Transition to the breast cancer health states:<br/>General population age-based breast cancer risk estimates (AIHW) multiplied by a constant relative risk increase (1.84; AIHW and Cuzick et al.) and a time-dependent relative risk reduction for tamoxifen (Cuzick et al.).</p> <p>Transition to the adverse events health states:<br/>Cuzick et al. (for endometrial cancer, venous thrombotic event and cataract) and Eckerman et al. (for cataract surgery).</p> <p>Transition to the death state:<br/>Age-based natural mortality rates (Australian Bureau of Statistics).<br/>Annual breast cancer mortality (AIHW).<br/>Adverse event-related mortality (AIHW, Shiraev et al., Cugati et al.).</p> |
| Costs                            | <p>Breast cancer: \$33,555 annually, from diagnosis until death (on average ~\$455,000 in total)</p> <p>Endometrial cancer: \$6,360 one-off</p> <p>Venous thrombotic event: \$6,540 one-off</p> <p>Cataract surgery: \$5,728 one-off</p> <p>GP visit: \$16.95</p> <p>Watchful waiting: \$237 annually</p> <p>Tamoxifen: ██████ monthly, for 5 years</p>  |
| Utilities                        | <p>Moderate to high risk women: 1.00</p> <p>Breast cancer: 0.77 (= -0.23 annually from diagnosis until death, on average ~-4.9 in total)</p> <p>Endometrial cancer: -0.087 one year</p> <p>Venous thrombotic event: -0.078 one year</p> <p>Cataract: -0.1 one year</p> <p>Cataract surgery: -0.1 one year</p>  |

Source: compiled during the evaluation.

6.16 The key drivers of the model are shown below.

Table 7: Key drivers of the model

| Description                                    | Method/Value   | Impact   |
|--|--|--|
| Adverse event assumptions                      | Adverse event related costs, disutilities and mortality last 1 year. | Possibly high impact. The model structure does not allow increased duration.<br>Favours tamoxifen. |
| Breast cancer costs                            | \$33,500 per year from diagnosis until death                         | High impact.<br>Favours tamoxifen.   |
| Breast cancer mortality                        | 0.03 per year from diagnosis until death                             | High impact.<br>Favours tamoxifen.   |
| Breast cancer utility                          | 0.77 from diagnosis until death                                      | Moderate impact.<br>Favours tamoxifen.   |
| Duration of treatment benefit with tamoxifen   | 20 years   | High impact.<br>Favours tamoxifen.   |
| Moderate to high risk of breast cancer utility | 1.0  | Moderate impact.<br>Favours tamoxifen.   |
| Risk modifier                                  | 1.84   | High impact.<br>High risk modifier favours tamoxifen.  |
| Time horizon                                   | Lifetime (70 years); extrapolated from 10 years                      | High impact.<br>Favours tamoxifen.   |

Source: compiled during the evaluation.

6.17 Table 8 presents the results of the stepped economic evaluation as performed in the submission. The results of this economic evaluation likely significantly underestimate the incremental costs and overestimate the incremental value of tamoxifen due to the overestimation of ER+ breast cancer costs, overestimation of breast cancer related disutility, underestimation of tamoxifen costs and underestimation of adverse event-related costs, disutilities and mortality.

Table 8: Results of the stepped economic evaluation as presented in the submission

| Step and component   | Tamoxifen | Placebo  | Increment |
|--|-----------|----------|-----------|
| Trial-based costs (tamoxifen cost based on dispensed price and adjusted for compliance) and outcomes (ER+ BC) (10 year time horizon, undiscounted) |           |          |           |
| Costs  | \$█       | \$0      | \$█       |
| ER+ BC   | 0.0154    | 0.0278   | -0.0124   |
| Incremental cost/extra ER+ BC avoided  |           |          | \$█       |
| Upper 95% CL (-0.009) of differences in outcome  |           |          | \$█       |
| Lower 95% CL (-0.0158) of differences in outcome   |           |          | \$█       |
| <b>10-years</b>  |           |          |           |
| Costs  | \$█       | \$6,555  | -\$█      |
| QALYs  | 7.97      | 7.97     | 0.01      |
| Incremental cost/QALY gained   |           |          | Dominant  |
| <b>20-years</b>  |           |          |           |
| Costs  | \$█       | \$17,382 | -\$█      |
| QALYs  | 12.57     | 12.53    | 0.04      |
| Incremental cost/QALY gained   |           |          | Dominant  |
| <b>Lifetime</b>  |           |          |           |
| Costs  | \$█       | \$30,418 | -\$█      |
| QALYs  | 16.22     | 16.12    | 0.10      |
| Incremental cost/QALY gained   |           |          | Dominant  |

Source: Table D.5-4, p132 of the submission.

6.18 From the submission, the ESC noted:

- The economic evaluation in the submission overestimated the costs for treating breast cancer. The submission assumed the costs for treating breast cancer to be \$33,500 per patient in each year subsequent to diagnosis (~\$455,000 in total before discounting). These costs were obtained from the literature, but these are total costs rather than annual costs. Conversely, the costs of managing the conditions with heightened risk due to tamoxifen (e.g. cataracts, endometrial cancer, and venous thrombotic events) are one-off costs and derived using AR-DRGs, yielding considerably lower cost estimates than the cost for breast cancer.
- Non-breast cancer adverse event-related disutility and mortality were only applied for one year (one model cycle), while breast cancer-related disutility and mortality were applied from breast cancer diagnosis until death. This is likely to significantly favour tamoxifen both in terms of costs and effectiveness. Due to the model structure, the commentary alternate scenario (see below) did not include alternative assumptions regarding the adverse event-related costs, disutilities and mortality. The alternate scenario may therefore still underestimate the ICER of tamoxifen compared to placebo.
- The economic evaluation assumed that the reduction in ER+ breast cancer incidence translates into a corresponding reduction in breast cancer mortality. This is not supported by the clinical evidence.
- The same overall breast cancer survival was used for ER+ breast cancer and 'other' breast cancer. ER+ breast cancer survival post-tamoxifen may differ from overall breast cancer survival, for example due to different treatment options.
- The submission assumed a utility value of 1.00 for women with a moderate to high risk of breast cancer, whereas a general population will have a mean utility of less than 1.00. Assuming a utility value for those without breast cancer of 1.00 overestimates the utility gain from preventing breast cancer, which favours

tamoxifen. The ESC considered that a utility score should at least align with general population for the proposed population, but noted the PSCR (p3) stated that using a score between 0.75 and 0.9 showed that tamoxifen remained dominant over watchful waiting (using the original model in the submission).

- In the economic evaluation, only the PBS contribution of the cost of tamoxifen (\$█████ per 30 tablet pack) was taken into account, favouring tamoxifen. The corresponding requested dispensed price per pack was \$█████. The PSCR (p3) reiterated that a price change for tamoxifen is not being proposed.
- In the economic model for the high risk group, the baseline risk as well as the efficacy of tamoxifen and age were based on subgroup analyses. It would be more appropriate to assume the efficacy of tamoxifen in the high risk subgroup is the same as the efficacy in the moderate to high risk subgroup, since there is not enough information to assume a difference. The current use of the subgroup efficacy increases the ICER and is therefore conservative. However, this potentially confounds the comparison of the ICERs for the high risk and moderate to high risk groups. Specifically the ICER for the high risk subgroup will be closer to that for the moderate to high risk group because it is assumed tamoxifen is less effective in high risk women. The ESC noted that effect endurance is assumed to last for longer (20 years) in the medium/high risk group than in the high risk subgroup (10 years). The PSCR (p3) stated that although the long-term breast cancer risk reduction is not as strong in the highrisk group, the sponsor considered it appropriate to use these data based on the high risk subgroup from the IBIS-I trial.

6.19 The evaluation presented an alternate scenario (including #1 and #2, below in Table 9) with alternate inputs in the model. The ESC noted the alternate scenario analysis presented in the evaluation. The ESC considered that the base case scenario should in addition include:

- corrected tamoxifen costs + jump state correction + half-cycle correction
- reduced breast cancer costs
- reduced breast cancer mortality.

6.20 The resulting ICER was less than \$15,000 per quality adjusted life year (QALY) gained ('ESC base case').

Table 9: 'ESC base-case' based on the alternate scenario presented in the evaluation.

|    |  | Tamoxifen + watchful waiting | Watchful waiting | Increment      |
|----|--|------------------------------|------------------|----------------|
| #0 | <b>Submission base-case</b>  |                              |                  |                |
|    | Costs  | \$ [REDACTED]                | \$30,418         | -\$ [REDACTED] |
|    | QALYs  | 16.22                        | 16.12            | 0.10           |
|    | Incremental cost/QALY gained   |                              |                  | Dominant       |
| #1 | <b>#0 + corrected tamoxifen costs + jump state correction + half-cycle correction</b><br>-Tamoxifen costs according to the dispensed price of tamoxifen (\$ [REDACTED]) rather than the PBS contribution (\$ [REDACTED]).<br>-Women in the "ER+ breast cancer" health state who developed cataract were returned to the "ER+ breast cancer" state, instead of the "other breast cancer" state.<br>-Half-cycle correction was performed.  |                              |                  |                |
|    | Costs  | \$ [REDACTED]                | \$30,299         | -\$ [REDACTED] |
|    | QALYs  | 15.72                        | 15.62            | 0.10           |
|    | Incremental cost/QALY gained   |                              |                  | Dominant       |
| #2 | <b>#1 + reduced breast cancer costs</b><br>The submission obtained the costs for treating breast cancer from the literature (Wong et al. 2008), but it is not clear from the literature if these costs represent annual or total breast cancer costs. In the submission these costs were assumed to be annual costs, resulting in high total breast cancer costs (~\$455,000 without discounting). In the alternate scenario, it was assumed the breast cancer costs of \$33,555 were total costs. In the alternate scenario, these total costs were applied at the moment of breast cancer diagnosis. |                              |                  |                |
|    | Costs  | \$ [REDACTED]                | \$8,112          | \$ [REDACTED]  |
|    | QALYs  | 15.72                        | 15.62            | 0.10           |
|    | Incremental cost/QALY gained   |                              |                  | \$ [REDACTED]  |
| #3 | <b>#2 + reduced breast cancer mortality</b><br>The annual probability to die from breast cancer was changed from 0.03 to 0.003, based on the relative risk of breast cancer mortality obtained from the Cuzick meta-analysis (0.97, 10 years), transformed to a 1-year transition probability ( $1 - 0.97 = 0.03 \rightarrow -(1/10) \cdot \ln(1 - 0.03) = 0.003 \rightarrow 1 - \exp(-0.003) = 0.003$ ).  |                              |                  |                |
|    | Costs  | \$ [REDACTED]                | \$8,113          | \$ [REDACTED]  |
|    | QALYs  | 15.84                        | 15.79            | 0.05           |
|    | Incremental cost/QALY gained   |                              |                  | \$ [REDACTED]  |

Source: compiled during the evaluation.

6.21 The ESC noted the univariate sensitivity analyses were performed on the alternate scenario, as presented in the evaluation, where ICERs ranged from dominant to more than \$200,000 per QALY gained with tamoxifen compared to placebo. The PSCR (p3) stated that reporting the ICER at a 10 year time horizon for an intervention designed to protect women from breast cancer over a lifetime is highly inappropriate, and the sponsor asserted that reporting such a broad range of ICERs from dominant to more than \$200,000 per QALY gained in sensitivity analyses does not inform quality decision making. The ESC noted that additional sensitivity analysis of the 'ESC base case', including varying the applications of utilities or varying the costs of treatments and adverse events, resulted in ICERs for tamoxifen relative to placebo ranging from dominant to dominated.

- 6.22 The ESC noted that the threshold of incremental QALYs gained previously accepted by the PBAC for treatments with large patient populations, such as population preventative interventions including lipid-lowering, anti-hypertensive drugs and vaccines, was at the lower end of the ICER range of \$15,000-\$45,000/QALY.

Table 10: Sensitivity analyses on the ESC base-case

|           |  | Tamoxifen + watchful waiting | Watchful waiting | Increment      |
|-----------|--|------------------------------|------------------|----------------|
| <b>#3</b> | <b>New ESC base-case (see table above)</b>   |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$8,113          | \$ [REDACTED]  |
|           | QALYs  | 15.84                        | 15.79            | 0.05           |
|           | Incremental cost/QALY gained   |                              |                  | \$ [REDACTED]  |
| <b>#4</b> | <b>#3 + general population utility value</b><br>The utility of women with a moderate to high risk of breast cancer was changed from 1.00 to 0.85, to reflect a general population.   |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$8,113          | \$ [REDACTED]  |
|           | QALYs  | 13.56                        | 13.55            | 0.01           |
|           | Incremental cost/QALY gained   |                              |                  | \$ [REDACTED]  |
| <b>#5</b> | <b>#3 + one-off impact on utility</b><br>In the submission, breast cancer disutility is applied continuously (from diagnosis until death), while adverse event disutility is applied for one cycle only. In this sensitivity analysis, breast cancer disutility is applied for only one cycle (=one year), consistent with adverse event disutilities.   |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$8,113          | \$ [REDACTED]  |
|           | QALYs  | 15.99                        | 16.00            | -0.00          |
|           | Incremental cost/QALY gained   |                              |                  | Dominated      |
| <b>#6</b> | <b>#3 + DRG costs for adverse events as well as breast cancer</b><br>In the submission, breast cancer costs were obtained from Wong et al. 2008, while adverse event costs were obtained from DRG costs. In this sensitivity analysis, breast cancer costs were obtained from DRG costs, in the same way this was done for adverse events (a weighted average from DRG codes J06A, J07A, J62A and J62B = \$7,232 for breast cancer). |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$3,499          | \$ [REDACTED]  |
|           | QALYs  | 15.84                        | 15.79            | 0.05           |
|           | Incremental cost/QALY gained   |                              |                  | \$ [REDACTED]  |
| <b>#7</b> | <b>#5 and #6 combined</b>  |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$3,499          | \$ [REDACTED]  |
|           | QALYs  | 15.99                        | 16.00            | -0.00          |
|           | Incremental cost/QALY gained   |                              |                  | Dominated      |
| <b>#8</b> | <b>#3 + alternative breast cancer costs</b><br>The submission obtained the costs for treating <u>stage I</u> breast cancer from the literature (Wong et al. 2008). This source presents breast cancer costs dependent on cancer stage. For this sensitivity analysis, breast cancer costs were changed from \$33,555 to \$71,287 (total costs for <u>stage III</u> breast cancer, Wong et al. 2008).                                 |                              |                  |                |
|           | Costs  | \$ [REDACTED]                | \$14,726         | -\$ [REDACTED] |
|           | QALYs  | 15.84                        | 15.79            | 0.05           |
|           | Incremental cost/QALY gained   |                              |                  | Dominant       |

- 6.23 The pre-PBAC response accepted the proposed 'ESC base case' of less than \$15,000/QALY gained, but believed this to be a conservative estimate of the ICER.

The PBAC noted that even with the ‘ESC base case’ many residual assumptions favoured tamoxifen, and so disagreed that this estimate is conservative. The Pre-PBAC Response argued that sensitivity analyses #5 and #7 are ‘highly inappropriate because the disutility associated with breast cancer is known to have an impact on women for multiple years (at least 5-10 years rather than just one year as the sensitivity analyses suggest)’. The PBAC considered that the most plausible and informative sensitivity analyses were #4 and #6, which resulted in ICERs of between \$15,000 and \$45,000 per QALY gained. The PBAC considered that these sensitivity analyses indicated ICERs within, but at the higher end of, the previously accepted cost-effectiveness range for a primary prevention strategy. The PBAC viewed that the ‘ESC base case’ of less than \$15,000/QALY gained may or may not be conservative, and that the PBAC preferred sensitivity analyses lie at the upper limits of the cost-effective range.

- 6.24 In the economic evaluation for the high risk subgroup (relative risk increase 3.76), the baseline risk as well as the efficacy of tamoxifen and age were based on subgroup analyses from the IBIS-I trial. Table 11 shows the relative risk of ER+ breast cancer for women treated with tamoxifen versus placebo in the high risk subgroup as compared to moderate to high risk women. The submission did not address the PBAC guidelines in discussing a subgroup analysis, including the plausibility of a variation in treatment effect, whether the hypothesis underpinning the analysis was developed before or after the trial data were collected, a statistical analysis of the variation in treatment effect and an account of the number of pre-specified subgroup analyses conducted. In the submission, tamoxifen was dominant in the high risk base-case as well as each of the sensitivity analysis. During the evaluation, the high risk scenario was performed without changing the efficacy of tamoxifen compared to the moderate/high risk group (i.e. only changing the baseline risk) and under the alternate scenario. Tamoxifen was still dominant over watchful waiting. As was the case in the alternate scenario for the moderate to high risk group, adverse event-related costs, disutilities and mortality were not revised and were therefore only applied for one year.

Table 11: ER+ invasive breast cancer, difference between groups, tamoxifen vs. placebo, RR (95% CI)

|                                      | Moderate to high risk women | Moderate risk subgroup        | High risk subgroup |
|--------------------------------------|-----------------------------|-------------------------------|--------------------|
| <b>Meta-analysis Cuzick</b>          |                             |                               |                    |
| 0-5 years                            | 0.53 (0.42-0.65)            | NR                            | NR                 |
| 5-10 years                           | 0.60 (0.47-0.78)            | NR                            | NR                 |
| 0-10 years                           | 0.55 (0.47-0.65)            | NR                            | NR                 |
| <b>IBIS-I trial</b>                  |                             |                               |                    |
| 0-5 years                            | 0.74 (0.51-1.07)            | 0.85 (0.56-1.27) <sup>a</sup> |                    |
| 5-10 years                           | 0.56 (0.35-0.87)            | 0.46 (0.27-0.78) <sup>a</sup> |                    |
| 0-10 years                           | 0.67 (0.51-0.87)            | 0.69 (0.50-0.94) <sup>a</sup> |                    |
| <b>RR used in the economic model</b> |                             |                               |                    |
| 0-5 years                            | 0.53                        | NR                            |                    |
| 6-10 years                           | 0.60                        | NR                            |                    |
| 11-20 years                          | 0.60                        | NR                            |                    |
| >20 years                            | 1.00                        | NR                            |                    |

Abbreviations: NR = not reported; RR = relative risk.

Source: Table C.4-2 of the submission, p81.

<sup>a</sup> Calculated based on the data in Table C.4-2 of the submission.

**Drug cost/patient/year for the proposed listing**

6.25 (2 months' supply per script, DPMQ \$ [REDACTED]): \$ [REDACTED] (drug cost/patient/5 year course: \$ [REDACTED]).

**Drug cost/patient/year for the alternative listing**

6.26 (1 month's supply per script, DPMQ \$ [REDACTED]): \$ [REDACTED] (drug cost/patient/5 year course: \$ [REDACTED]).

6.27 The proposed PBS listing as well as the majority of the guidelines and clinical trials, suggest a maximum of five years of treatment.

**Estimated PBS usage & financial implications**

6.28 This submission was considered by DUSC. The base case (Method 1) and sensitivity analysis (Method 2) financial impact analyses presented in the submission both take an epidemiological approach. For the base-case calculations, information about uptake was obtained from the 2010 National Health Interview Survey from the USA. The survey estimated that 0.03% of women aged 35 to 79 years were taking tamoxifen and 0.21% of women aged 50 to 79 years were taking raloxifene for primary prevention of breast cancer. It was assumed that the women aged 50 to 79 years that were taking raloxifene in the survey would take tamoxifen in the Australian context where raloxifene is not available. Uptake was assumed to be 0.03% for women aged 35 to 79 years and 0.21% for women aged 50 to 79 years. Overall, these proportions results in an uptake of ~0.16% of Australian women aged 35-79 years. It is unknown to what extent tamoxifen uptake in Australia will be similar to tamoxifen uptake in the USA. Population projections of the number of women in Australia in 2016 to 2020 were sourced from the Australian Bureau of Statistics population projection. Treatment adherence was not taken into account.

Table 12: Estimated use and financial implications

|   | Year 1<br>2016 | Year 2<br>2017 | Year 3<br>2018 | Year 4<br>2019 | Year 5<br>2020 |
|---|----------------|----------------|----------------|----------------|----------------|
| <b>Estimated extent of use</b>            |                |                |                |                |                |
| Number treated                            | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     |
| Scripts <sup>a</sup>                      | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     |
| <b>Estimated net cost to PBS/RPBS/MBS</b> |                |                |                |                |                |
| Net cost to PBS/RPBS                      | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |
| Net cost to MBS                           | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |
| <b>Estimated total net cost</b>           |                |                |                |                |                |
| Net cost to PBS/RPBS/MBS                  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |

<sup>a</sup> Assuming 12 scripts per year as estimated by the submission. Assuming 100% adherence.  
Source: Section E.4 and E.5, pp141-141 of the submission.

6.29 At year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be less than \$10 million. The net five-year cost to the PBS in the submission was less than \$10 million. Sensitivity analyses explored the impact of calculating the expected use of tamoxifen with uptake based on other sources (NHRMC clinical practice guidelines, percentage of women attending BreastScreen Australia and tamoxifen uptake in a family health clinic in the UK) and of increasing uptake over the years (with 0.01% increase per year, 0.02% increase per year and

0.03% increase per year). The net five-year costs to the PBS of these analyses ranged from less than \$10 million in the first sensitivity analysis (uptake based on other sources) to \$10 - \$20 million in the sensitivity analysis with 0.03% increase in uptake per year. The accuracy of the results from the base-case as well as the sensitivity analyses is unknown since the expected uptake of tamoxifen is highly uncertain.

- 6.30 The submission did not provide financial forecasts for the high risk only group.
- 6.31 The submission did not consider MBS costs related to baseline assessments (e.g. pre-tamoxifen gynaecologic assessment), specialist evaluation of adverse events (e.g. evaluation of gynaecological symptoms) and GP and/or specialist treatments of adverse events. This underestimated the impact of tamoxifen use to the MBS by an unknown amount.
- 6.32 DUSC considered that:
- There is a lack of good epidemiological data for determining the number of people at increased risk of breast cancer in Australia. Although the size of the population at moderate to high risk of developing breast cancer and uptake of tamoxifen in this group is difficult to predict, the DUSC considered that triangulation of both methods presented in the submission was appropriate to reduce this uncertainty.
  - Many different risk algorithms exist to assess breast cancer risk. The recommended or acceptable risk calculators are not specified in the restriction. This increases the uncertainty of the population that will be treated. Four different methods of calculating risk were used in the clinical trials.
  - Some patients may continue tamoxifen beyond five years given its place in the prevention of breast cancer.
  - Not all of the estimated 0.21% of women aged 50 to 79 years that were taking raloxifene in the US context would take tamoxifen in the Australian context. This is because a benefit/risk analysis indicated that raloxifene displayed a better benefit-to-risk profile than tamoxifen for postmenopausal women with a uterus. DUSC considered that there may be some women in Australia taking PBS subsidised raloxifene for osteoporosis who are also at moderate to high risk of breast cancer. This means the patient numbers in the submission may be overestimated.
  - Conversely, using the US Survey figures may underestimate the number of women that will take tamoxifen in the Australian context as the US does not have universal health insurance coverage. Even though tamoxifen is not expensive, the cost may still be a barrier to some women without insurance in the US.
  - When calculating the number of eligible patients, the submission did not take into account women aged <35 years (consistent with the USA study). Since the requested PBS listing does not provide an age limit, the actual number of eligible women may be higher (i.e. the submission estimate of patients may be an underestimate).
  - Method 2 only estimated patients based on the number of Australian women aged 40 to 60 years rather than the age range of 35 to 79 years used in Method 1. Thus Method 2 is an underestimation of the number of eligible women.
  - The estimate of the percentage of women actively monitoring breast cancer in Method 2 (ie. 54.6%) may be an underestimate as not all would be captured in the BreastScreen Australia data.

- The assumption in both Methods 1 and 2 that the uptake rate would be constant across Years 1 to 5 was considered to be unlikely.
  - Some patients may already be receiving tamoxifen for primary prevention on private prescription and may continue to access the medicine this way after PBS listing (particularly general patients). The DUSC Secretariat has estimated from Price Disclosure data that the private market for tamoxifen was approximate 8% of the tamoxifen market in the most recent year of available data (i.e. October 2014 to September 2015). If these private patients are taking tamoxifen for reduction of breast cancer risk it is estimated there would be approximately 1,500 patients taking tamoxifen for reduction of breast cancer risk in this period.
  - Twelve prescriptions per year are assumed in the submission. This does not take into account treatment adherence which was estimated to be 70%. Therefore, there is a potential for the number of prescriptions per woman to be less than the estimate in the submission.
- 6.33 Overall, the DUSC advised that the likelihood and possible extent of usage beyond the requested restriction is low. The variable methods of calculating “moderate to high risk of breast cancer” may lead to some usage beyond expectations. It is unlikely that tamoxifen would be used in patients at average risk of breast cancer given the risk of increased endometrial cancer, DVT/thrombotic events and cataracts.
- 6.34 The submission’s estimate of the uptake of tamoxifen was based on the 2010 National Health Interview Survey (USA). Overall, the DUSC advised that this estimate is highly uncertain because it is unknown to what extent USA uptake is similar to the expected uptake in Australia. Based on the data from the USA, uptake in Australia was assumed to be 0.16% of women aged 35-79 years. However, the potential uptake is considerably higher than 0.16% in Australia.
- 6.35 DUSC considered the uptake of tamoxifen for the reduction of risk of breast cancer is uncertain, but considered the estimates to be reasonable based on the available information and triangulation of two methods.

### **Quality Use of Medicines**

- 6.36 The submission did not address possible quality use of medicines issues with the use of tamoxifen for the prevention of breast cancer e.g. optimal timing of treatment start for premenopausal women, appropriate counselling and follow-up.
- 6.37 The submission proposed a maximum quantity of 60 tablets (2 months’ supply per script) and an alternative of 30 tablets per script. In case of 60 tablets per script, patients would only have to pay a co-payment once every 2 months instead of once every month. Furthermore, the maximum quantity of 60 tablets would allow a total of 12 months’ supply of tamoxifen which the submission stated would align with the annual clinical review for watchful waiting. The submission suggested that the standard 6-month supply could result in poor compliance should these women fail to visit their GP for a repeat prescription. However, a 6-month period may allow for closer monitoring of possible side effects.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## 7 PBAC Outcome

- 7.1 The PBAC recommended a Restricted Benefit listing of tamoxifen for the reduction of breast cancer risk in patients at moderate to high lifetime risk of breast cancer, on the basis of acceptable cost-effectiveness compared to watchful waiting.
- 7.2 The PBAC noted the proposed restriction in the submission and the suggestions by the Secretariat. The PBAC also noted that DUSC considered that more frequent review may assist in detection and management of adverse events and encourage compliance. The PBAC advised that the PBS restriction wording should be finalised after completion of the registration of this drug by the TGA and the entry in the Australian Registry of Therapeutic Goods is known. The PBAC agreed with DUSC that regular review of patients would be advantageous and recommended a maximum quantity of 30 x 20 mg tamoxifen with 5 repeats, but considered that the frequency of review for primary prophylaxis would not be driven by the restriction, but rather by good clinical practice.
- 7.3 The PBAC accepted that the proposed place of tamoxifen for this listing is in the reduction of breast cancer risk, in patients with moderate to high risk of developing breast cancer. A patient was considered at moderately increased risk of developing breast cancer if their lifetime breast cancer risk is 1.5 to 3 times the population average. A patient was considered at high risk if their lifetime breast cancer risk is more than 3 times the population average. The PBAC noted that the patient population was crudely defined. This was because most risk calculators are imperfect predictors of future disease and age-specific relative risk is of greater relevance than lifetime risk. The PBAC anticipated that specialist prescribers of tamoxifen would consider these factors prior initiating treatment. Patients would be eligible for five years of PBS-subsidised therapy.
- 7.4 The PBAC considered that 'watchful waiting' was the appropriate comparator for patients at both moderate and high risk of breast cancer. The PBAC noted that preventive surgery may be considered by some high risk women, but considered that only a small proportion of women choose this option, and that 'watchful waiting' is therefore the therapy most likely to be replaced in practice.
- 7.5 The PBAC noted that the clinical evidence presented to support the submission was a meta-analysis of four head-to-head trials (IBIS-I, NSABP-1, Marsden, Italian) comparing tamoxifen to placebo and included 28,444 trial participants.
- 7.6 The PBAC noted the heterogeneity between trials in the size of the effect, but overall agreed that tamoxifen is clinically superior to placebo in reducing the incidence of breast cancer and inferior to placebo in terms of comparative safety. The PBAC agreed that clinical superiority was adequately supported in terms of the incidence of breast cancer but not in terms of survival:
- Based on the meta-analysis by Cuzick et al. (2013), tamoxifen reduces the incidence of invasive ER+ breast cancer in women at elevated risk. Tamoxifen did not significantly reduce breast cancer mortality or all-cause mortality.

- Tamoxifen is inferior in terms of safety due to an increased incidence of endometrial cancer, thromboembolic events and cataracts.
- 7.7 The PBAC agreed with the ESC that several inputs into the modelled economic evaluation presented in the submission were unreasonable or overly optimistic (in favour of tamoxifen), including the tamoxifen costs, breast cancer costs, and breast cancer mortality. The PBAC considered the revised 'ESC base-case' to be reasonable (with a resulting Incremental Cost per QALY gained of less than \$15,000 per QALY gained), but viewed the sensitivity analyses #4 and #6 to represent the most plausible and informative analyses for its decision-making. These analyses adjusted the utility of women with a moderate to high risk of breast cancer was from 1.00 to 0.85, to reflect a general population; and applied revised breast cancer costs obtained from DRG costs (which had been used for the adverse events costs), rather than from Wong et al. 2008. The resulting Incremental Cost per QALY gained ranged between \$15,000 and \$45,000. The PBAC considered these to lie within the previously accepted cost-effectiveness range for a primary prevention strategy.
- 7.8 The PBAC noted that at year 5, the estimated number of patients was more than 10,000 and the net cost to the PBS would be less than \$10 million. The PBAC agreed with the DUSC advice that the utilisation estimates are uncertain, and considered that the total additional cost estimates were uncertain and highly dependent on the patterns of uptake and treatment continuation when tamoxifen is available for this preventative indication. However, it considered that the utilisation was unlikely to have been underestimated, and that net costs to the PBS were unlikely to be higher than estimated in the application.
- 7.9 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that tamoxifen for the reduction of breast cancer risk should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.10 The PBAC noted that tamoxifen for the treatment of breast cancer is currently included on the PBS for prescribing by nurse practitioners under a Shared Care Model. The PBAC advised that tamoxifen for the reduction of breast cancer risk is suitable for prescribing by nurse practitioners under the Continuing Therapy Only model where prescribing of medicine for a patient has been initiated by a medical practitioner.
- 7.11 The PBAC recommended that the Early Supply Rule should apply, as it is the case for the listing for the treatment of breast cancer.
- 7.12 The PBAC noted that flow-on restriction changes are required since the current tamoxifen listings include the following Administrative Advice: "This drug is not PBS-subsidised for primary prevention of breast cancer." In addition, the PBAC noted that the existing listings for tamoxifen are for a PBS Indication of "Breast cancer". The PBAC recommended that this restriction should be amended to clarify that the listing is for the treatment of breast cancer.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Restriction to be finalised, following finalisation of TGA registration details.

| Name, Restriction,<br>Manner of administration and form | Max.<br>Qty<br>Units | No. of<br>Rpts | Proprietary Name and Manufacturer |             |
|---|----------------------|----------------|-----------------------------------|-------------|
| TAMOXIFEN<br>20 mg tablet, 30                           | 30                   | 5              | Noxaldex-D                        | AstraZeneca |

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 10 Sponsor's Comment

The sponsor had no comment.