

**6.07 GOSERELIN
3.6 mg implant
Zoladex Implant[®],
Astra Zeneca Pty Ltd.**

Application submitted by Medical Oncology Group of Australia

1 Purpose of Application

1.1 The minor submission requested a change to the current PBS restriction for goserelin 3.6 mg implant to enable women with hormone receptor negative breast cancers to access this treatment to reduce chemotherapy-induced menopause.

2 Requested listing

2.1 The submission did not provide a proposed restriction

Suggested wording for the restriction:

2.2 The Secretariat proposed the following changes to the existing restriction. Changes to the existing listing are indicated in italics and strikethrough for deletions.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
GOSERELIN 3.6 mg, implant	1	5	\$ [REDACTED]	Zoladex Implant	Astra Zeneca
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 <input type="checkbox"/> Midwives				
Condition:	Breast cancer				
PBS Indication:	Breast cancer				
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit				
Clinical criteria:	• The condition must be hormone receptor positive				

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

3 Background

3.1 Goserelin 3.6 mg implant is TGA registered for prostate cancer, endometriosis, uterine fibroids, endometrial thinning, assisted reproduction, and treatment of advanced breast cancer (T3b, T4 or any T with N2, 3 or M+) in premenopausal women suitable for hormonal manipulation (PI, p11).

- 3.2 At the November 2014 PBAC meeting, the PBAC agreed to a request from the Medical Oncology Group of Australia (MOGA) to have the drugs anastrozole, everolimus, exemestane, goserelin and letrozole made available to males with breast cancer on equity grounds. The PBAC recommended amending the restrictions for these five drugs and their breast cancer indications in such a way that male patients were not precluded from access to subsidy. Specifically in relation to goserelin, the PBAC noted that it would be unlikely that goserelin would be prescribed for post-menopausal women and so recommended that the restriction need not refer to menopausal status. The relevant amendments were effective from 1 March 2015.
- 3.3 At the December 2014 special meeting, as part of its consideration of the Post-Market Review of Authority listings, the PBAC recommended that goserelin be listed as a Restricted Benefit.
- 3.4 At the March 2015 meeting, the PBAC recommended that the restriction for goserelin implant 3.6 mg be amended to enable the treatment of hormone receptor positive breast cancer without restriction to cancer stage or chemotherapy use (March 2015 12.01).

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

4 Clinical place for the proposed therapy

- 4.1 The submission proposed that the restriction for goserelin be amended to enable women with hormone receptor negative breast cancers to access treatment in order to reduce chemotherapy-induced menopause. The submission indicated that this treatment is endorsed by the US National Comprehensive Cancer Network and in the St Gallen *Guidelines on Primary Therapy for Early Breast Cancer*.
- 4.2 The PBAC considered that it was appropriate for women undergoing chemotherapy that may affect fertility to access treatments that can reduce the risk of chemotherapy-induced menopause. However, the PBAC considered that the type of cancer was unlikely to influence the efficacy of goserelin in preserving fertility and therefore considered that it may not be reasonable or equitable to restrict the place in therapy to women with breast cancer only.

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

5 Comparator

- 5.1 The minor submission did not nominate a comparator for the clinical evidence.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input received from the Breast Cancer Network Australia via the Consumer Comments facility on the PBS website. The comments supported making goserelin available to premenopausal women with hormone receptor negative breast cancer who are undergoing chemotherapy. The PBAC specifically noted the advice that preservation of fertility is very important to many premenopausal women who may wish to start or grow their family, and may otherwise become infertile as a result of their treatment.

Clinical trials

6.3 The submission referred to one clinical trial and one meta-analysis (see Table 1).

Table 1: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
S0230	Goserelin in Preventing Ovarian Failure in Women Receiving Chemotherapy for Breast Cancer	Moore, <i>et al. NEJM.</i> 2015;372:923-32
Meta-analysis		
-	Ovarian suppression using luteinizing hormone releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies	Lambertini <i>et al. Ann Oncol.</i> 2015; 26: 2408-19

Source: Submission

Comparative effectiveness

6.4 The published data from trial S0230 showed that for the 135 (of 218) patients with complete primary end-point data, the ovarian failure rate was 8% in the goserelin group and 22% in the chemotherapy-alone group (odds ratio, 0.30; 95% confidence interval, 0.09 to 0.97; two-sided $p = 0.04$). Among the 218 patients who could be evaluated, pregnancy occurred in more women in the goserelin group than in the chemotherapy-alone group (21% vs. 11%, $p = 0.03$); women in the goserelin group also had improved 4 year Kaplan-Meier estimated disease-free survival ($p = 0.04$) and overall survival ($p = 0.05$).

6.5 From the Lambertini 2015 publication, 7 of the 12 trials included in the meta-analysis used goserelin as the luteinizing hormone-releasing hormone agonist (LHRHa) treatment. The meta-analysis indicated:

- A significant reduced risk of premature ovarian failure (POF; OR 0.36, 95% CI 0.23–0.57; $p < 0.001$), yet with significant heterogeneity ($I^2 = 47.1\%$, $p_{\text{heterogeneity}} = 0.026$).
- In eight studies reporting amenorrhea rates 1 year after chemotherapy completion, the addition of LHRHa reduced the risk of POF (OR 0.55, 95% CI

- 0.41–0.73, $p < 0.001$) without heterogeneity ($I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.936$).
- In five studies reporting pregnancies, more patients treated with LHRHa achieved pregnancy (33 versus 19 women; OR 1.83, 95% CI 1.02–3.28, $p = 0.041$; $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.629$).
 - In three studies reporting disease-free survival, no difference was observed (HR 1.00, 95% CI 0.49–2.04, $p = 0.939$; $I^2 = 68.0\%$, $p_{\text{heterogeneity}} = 0.044$).
- 6.6 The PBAC noted that the group of patients taking goserelin experienced a reduction in the rate of ovarian failure and a higher rate of pregnancy, and that it did not appear to affect disease-free survival. The PBAC noted that the consumer comments indicated that pregnancy rate was an important outcome for patients.

Comparative harms

- 6.7 Trial S0230 showed that for the 111 patients who could be evaluated for adverse events in the chemotherapy-alone group, 6 had grade 3 toxic effects and none had grade 4 toxic effects. Of the 103 patients who could be evaluated for adverse events in the goserelin group, 1 had a grade 4 toxic effect (thromboembolism) and 6 had grade 3 toxic effects. Overall, 5% of the patients in the chemotherapy alone group and 7% in the goserelin group had grade 3 or higher toxic effects ($P = 0.89$), 24% and 48% had grade 2 or higher toxic effects, respectively ($p < 0.001$).
- 6.8 The meta-analysis did not report on comparative harms.

Economic analysis

- 6.9 The minor submission did not present an economic comparison. The PBAC noted that although no evaluation of the cost-effectiveness of fertility preservation was presented, it would be difficult to determine the value of retained fertility or pregnancy and children. The PBAC further considered that as the efficacy of goserelin is unlikely to be affected by the type of cancer, it would be reasonable that the cost-effectiveness would be similarly unaffected.

Drug cost/patient/course: \$ [REDACTED]

- 6.10 The drug cost per patient is based on a maximum course of treatment of 6 months, as the submission estimates that treatment in this setting will be for 3-6 months duration only. The PBAC noted that the pre-PBAC response estimated that 30% of patients would have a treatment duration of 3 months, which would result in a cost of \$ [REDACTED] per patient per course.

Estimated PBS usage & financial implications

- 6.11 The minor submission estimated that up to an additional less than 10,000 patients per year would use goserelin for 3 to 6 months if the proposed change is recommended. At the upper estimate of less than 10,000 patients using goserelin for 6 months, this would result in a net cost to the PBS of less than \$10 million in each year of listing, with a total net cost to the PBS of less than \$10 million over the first 5 years of listing.

Table 2: Total cost to the PBS for the use of goserelin

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Number of patients	█	█	█	█	█	█
Total cost to PBS	\$█	\$█	\$█	\$█	\$█	\$█
Total co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS	\$█	\$█	\$█	\$█	\$█	\$█

Source: prepared by HTA based on submission assumption of up to █ patients per year.

- 6.12 The pre-PBAC response estimated that approximately 30% of patients would only receive treatment for 3 months.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision regarding amending the current listing of goserelin 3.6 mg implant to allow for PBS-subsidised access for the preservation of fertility in premenopausal women with breast cancer undergoing chemotherapy, on the basis that patient populations in addition to that proposed by MOGA may benefit from and use this treatment. Consequently the utilisation may be underestimated.
- 7.2 The PBAC recognised the clinical need for and benefits of preserving fertility in premenopausal women undergoing chemotherapy. However, the PBAC considered that this clinical need was relevant to all premenopausal women undergoing chemotherapy, and that the submission's proposal to restrict use to only patients with breast cancer was inequitable.
- 7.3 The PBAC noted that the submission did not nominate a clinical comparator, and considered that this was appropriate as there are no other treatment options available.
- 7.4 The PBAC noted that patients taking goserelin had a reduced rate of ovarian failure and an increased rate of pregnancy. The PBAC considered that although the evidence presented in the submission related to breast cancer only, there was no evidence to indicate that the efficacy of goserelin in preserving fertility would be affected by the type of cancer. The PBAC considered that gonadal toxicity was related to the type of drug, the dose administered, use as combination agents and duration of use. Also important for some cancers was whether treatment involved radiation fields which included the ovaries at a dose which was likely to be toxic. Patient factors, particularly age of exposure to treatment, was also a consideration in identifying patients who may benefit.
- 7.5 The PBAC considered that there was a high risk of use by patients with other cancers and therefore the proposed utilisation was an underestimate. However, the PBAC considered that this use may be clinically appropriate. The PBAC also considered that there was minimal risk of use beyond the estimated treatment period due to the menopausal side effects of treatment.

- 7.6 The PBAC also considered that there was an insufficient evidence base to support the patient numbers or estimated duration of treatment estimated in the submission, and therefore the cost of listing was uncertain.
- 7.7 Rather than prevent leakage into all patients for whom goserelin may prevent chemotherapy-induced menopause from occurring, the PBAC considered that a resubmission should present a revised proposal for this broader patient population, which should include a revised restriction and utilisation estimates to more accurately reflect the appropriate clinical place in therapy (refer to paragraph 7.4). The PBAC also noted that because of the uncertain utilisation, it may be necessary to include a risk share arrangement cap on patient numbers.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

The Association is disappointed at the deferral and are currently reviewing the PBAC's advice in relation to the available evidence on fertility preservation for premenopausal women.