PUBLIC SUMMARY DOCUMENT
Product: Goserelin acetate, subcutaneous implant, 3.6 mg (base) in pre-filled injection syringe, Zoladex Implant®,
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought to extend the current Authority Required listing to include use in hormone dependent early breast cancer in peri or pre-menopausal women.

2. Background

Goserelin acetate 3.6 mg subcutaneous implant has not previously been considered by the PBAC for the treatment of hormone receptor positive early stage breast cancer in peri or premenopausal women.

3. Registration Status

Goserelin acetate 3.6 mg subcutaneous implant was TGA registered on 14 October 1991. It is indicated for:

- Prostate cancer (palliative; adjuvant, neoadjuvant therapy with radiotherapy for locally advanced prostate cancer);
- Advanced breast cancer (premenopausal women);
- Early breast cancer (adjuvant)-perimenopausal and premenopausal women;
- Symptomatic control in proven endometriosis;
- Uterine fibroids (selected cases);
- Endometrial thinning prior to ablation;
- Pituitary down regulation prior to controlled ovarian superstimulation

4. Listing Requested and PBAC's View

Changes to the current listing are highlighted in bold, italics and strikethrough.
Authority required
Locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate
Hormone-dependent ~~locally advanced (equivalent to stage III) or metastatic (equivalent to stage IV)~~ breast cancer in ***peri or*** pre-menopausal women;
Short-term treatment (up to 6 months) of visually proven endometriosis (only 1 course of not more than 6 month's therapy will be authorised).

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Approximately 60% of breast cancer tumours in premenopausal women are hormone sensitive (oestrogen or progesterone receptor positive). These patients may be suitable for hormonal treatment. The goal of hormonal therapy is to reduce the availability of oestrogen/progesterone to the cancer cell to reduce tumour growth. This can be achieved by combination chemotherapy, blocking oestrogen receptors with drugs such as tamoxifen, suppression of oestrogen synthesis by luteinising hormone releasing hormone (LHRH) agonists such as goserelin or ovarian ablation either surgically (oophorectomy) or by radiotherapy. In women who retain their hormone function after chemotherapy, tamoxifen and/or LHRH agonists are given alone or in combination to reduce circulating oestrogen levels.

Goserelin acetate 3.6 mg provides an alternative to combination chemotherapy or irreversible ovary ablation (via oophorectomy or radiotherapy) for the treatment of hormone dependent early breast cancer for peri or premenopausal women.

6. Comparator

The submission nominated the main comparator as chemotherapy. A secondary comparison with oophorectomy (either before or after chemotherapy) was also provided.

The submission stated there are insufficient data to compare goserelin to tamoxifen in this setting. However, a summary of data available comparing the use of LHRH analogues in combination with tamoxifen as an alternative to chemotherapy was presented.

The submission stated that the main difference between goserelin 3.6 mg and either chemotherapy or oophorectomy is that goserelin induces a menopausal status that may be reversible on cessation of therapy. This may enable younger women with early breast cancer to resume menses and possibly conceive after their adjuvant breast cancer treatment is completed.

7. Clinical Trials

The submission acknowledged that the majority of clinical data comparing goserelin and chemotherapy as adjuvant therapies in early breast cancer (EBC) uses the CMF chemotherapy regimen [cyclophosphamide, methotrexate, 5-fluorouracil] which is no longer widely used in clinical practice.

Anthracycline based chemotherapy regimens have now become the standard of care: e.g. doxorubicin and cyclophosphamide (AC), doxorubicin, cyclophosphamide, docetaxel (TAC), fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-D), fluorouracil, epirubicin, and cyclophosphamide (FEC).

The submission presented the results of two meta-analyses as follows:
Clinical evidence of the use of LHRH analogues in hormone receptor positive EBC in peri or premenopausal women:

- LHRH-agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Cuzick et al (2007) The Lancet 2007 May 19; 369 (9574):1711-23.

The meta-analysis from Cuzick et al (2007) used data from 11 906 women from sixteen clinical trials, the majority of whom used goserelin (10 040 patients) as the LHRH analogue and the remainder randomised to triptorelin or leuprorelin. Patients were node negative or node positive. The majority of trials were not blinded to treatment allocation as they were comparing combination intravenous chemotherapy with or without a subcutaneously implanted tablet (goserelin) and/or an oral tablet (tamoxifen). Four trials in the meta-analyses compared LHRH analogues to chemotherapy (CMF).

- Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women (Cochrane Review). Cochrane Database of Systemic Reviews 2008; (4): 1-29.

The Cochrane review contained data from 14 randomised trials containing nearly 12,000 women and was consistent with the data included in the Cuzick meta-analysis.

Clinical evidence on the use of ovarian ablation by surgery or irradiation:
The submission presented a meta-analysis of the following data examining ovarian ablation by surgical removal (oophorectomy) or irradiation to enable a comparison between goserelin and oophorectomy:

Early Breast Cancer Trialists' Collaboration Group. Ovarian ablation in early breast cancer: Overview of the randomised trials. The Lancet 1996 November 1; 348:1189-96

This series of meta-analyses examined the long term outcome (up to 15 years) of the patients randomised to clinical trials between 1948 and 1985. Data from almost 1200 women 50 years or younger were included (this age limit was designed to capture peri and premenopausal women as menopausal status was not consistently defined).

The submission provided the following published references:

Trial/First author	Protocol title/Publication title	Publication citation
Cuzick et al, 2007	LHRH-agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials.	The Lancet 2007 May 19; 369 (9574):1711-23.
National Breast Cancer Council	Clinical Practice Guidelines-Management of Early Breast Cancer (Second edition). 2001.	
Sharma et al, 2008	LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women (Cochrane Review).	Cochrane Database of Systemic Reviews 2008; (4):1-29.
Early Breast Cancer Trialists' Collaboration Group.	Ovarian ablation in early breast cancer: overview of the randomised trials.	The Lancet 1996 November 1; 348:1189-96.
Goldhurst A et al, 2009	Thresholds for Therapies: highlights of the St Gallen International Expert consensus on the Primary therapy of Early Breast Cancer 2009.	Annals of Oncology Advance Access 2009 June 17.
Partridge AH et al 2001	Side Effects of Chemotherapy and Combined Chemohormonal therapy in Women with Early-Stage Breast Cancer.	Journal of the National Cancer Institute Monographs 2001; 30:135-42.
Tham Y-LM et al, 2007	The Rates of Chemotherapy-Induced Amenorrhea in Patients Treated with Adjuvant Doxorubicin and Cyclophosphamide Followed by a Taxane.	American Journal of Clinical Oncology 2007 April 2; 30 (2):126-32.
Department of Health and Ageing	Intravenous Chemotherapy Supply Programme Guidelines.	Canberra; 2009 Feb 10.
Cancer Institute NSW	Cancer Institute of NSW Standard Cancer Treatments Website	https://www treatmentcancerinstituteorgau/cancerinstitute/cancerinstituteDAD

Trial/First author	Protocol title/Publication title	Publication citation
		AServlet?sid=2386376CIS&ent=1ES100&page=5BENPC&TopTab=Heal&AcceptHPTerms=true 2009.
Smith TJ et al, 2006	2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.	Journal of Clinical Oncology 2006 January 1; 24(19).
Do KA TS et al, 1998	Predictive factors of age at menopause in a large Australian twin study.	Human Biology 1998; 70(6):1073-91.
Morabia A et al, 1998	Collaborative study of neoplasia and steroid contraceptives. International variablility in ages at menarche, first livebirth and menopause.	American Journal of Epidemiology 1998 January 1; 148(12):1195-205.
National Breast and Ovarian Cancer Centre and Royal Australasian College of Surgeons	National Breast Cancer Audit: Public Health Monitoring Series 2007 data. Surry Hills, NSW	NBOCC; 2009

8. Results of Trials

The following comparisons were presented in the submission:

1a. LHRH analogue compared to chemotherapy.

A meta-analysis of the data comparing LHRH analogues (mostly consisting of goserelin data) was presented by Cuzick et al in 2007.

The submission stated that when used as adjuvant treatment in hormone receptor positive early breast cancer, LHRH analogues were equally efficacious as chemotherapy in preventing recurrence of breast cancer (HR 1.04, 95 % CI 0.92-1.17, p=0.52) and preventing death after recurrence of breast cancer (HR 0.93, 95 % CI 0.79-1.10, p=0.40).

The Cuzick et al (2007) meta-analysis did not undertake a comparison of the side effect profile of chemotherapy and LHRH analogues though the Cochrane Review stated hormonal therapy has fewer distressing side effects compared to chemotherapy. The incidence of menopausal side effects (hot flushes, vaginal dryness etc) was similar in both treatment groups, however women randomised to the chemotherapy group also experienced nausea and alopecia.

Quality of Life assessments included in the Cochrane review show goserelin improves QoL compared to chemotherapy in the first six months, but these differences do not continue beyond the first year of therapy.

1b. LHRH analogue in combination with tamoxifen compared to chemotherapy.

Where goserelin is used as an alternative to chemotherapy it can be used in combination with tamoxifen. The submission stated that a meta-analysis of three studies using this treatment scenario by Cuzick et al showed LHRH analogues used in combination with tamoxifen are more effective than chemotherapy alone. This did not reach significance (for recurrence of breast cancer; HR 0.90, 95 % CI 0.75-1.08, p=0.25 for death following recurrence; HR 0.89, 95 % CI 0.69-1.15, p=0.37).

The main side effect experienced by patients randomised to the goserelin and tamoxifen combination was hot flushes (91 %). The side effects of chemotherapy were as anticipated; nausea (81 %), alopecia (55 %) and hot flushes (54 %).

1c. Use of LHRH agonist with tamoxifen compared to tamoxifen alone.

The submission stated that the addition of an LHRH analogue to tamoxifen reduced the rate of recurrence compared to tamoxifen alone (HR 0.85, 95 % CI 0.67-1.09, p=0.20) and death following recurrence (HR 0.84, 95 % CI 0.59-1.19, p=0.33). The results were not significant. More side effects were experienced by the women randomised to the goserelin and tamoxifen combination (65 %) than tamoxifen alone (56 %). The most common side effects were hot flushes (44 % versus 26 %) and weight gain (11 % versus 4 %).

1d. Use of tamoxifen or LHRH agonist alone as adjuvant treatment of EBC in premenopausal women.

Cuzick et al did not compare the use of goserelin 3.6 mg or tamoxifen therapy alone as adjuvant treatment of hormone receptor positive EBC. The Cochrane Review reported the results of two small trials (320 patients and 187 patients) randomised to either goserelin or tamoxifen. The submission stated that no significant difference was reported by either trial in rate of recurrence, or death following recurrence, between patients randomised to goserelin or tamoxifen. A greater incidence of side effects was reported by the goserelin treated women.

2a. Use of an LHRH analogue following chemotherapy in younger women as an alternative to oophorectomy.

Younger women are more likely to retain their hormone function following chemotherapy, particularly when newer chemotherapy agents such as anthracycline based chemotherapy are used. The valid treatment options for women not rendered post menopausal following chemotherapy are using a LHRH analogue or oophorectomy to cease production of oestrogen/progesterone.

The submission stated that Cuzick et al showed for women below 40 years of age with hormone receptor positive EBC who had received chemotherapy (with or without tamoxifen) the subsequent use of goserelin significantly improved their outcomes. Rate of recurrence reduced by 25 % (95 % CI -39.4 to -7.7, p=0.01), the rate of death after recurrence reduced by 28 % (95 % CI -44.9 to -6.8, p=0.01). For women over 40 years of age (with a higher likelihood of being rendered post menopausal by chemotherapy), the subsequent use of goserelin did not significantly reduce the rate of breast cancer recurrence or death following recurrence.

The submission claimed that goserelin 3.6 mg is an efficacious treatment option for women who retain their hormone function following chemotherapy.

The submission stated that no data exist for the treatment setting following chemotherapy to allow a comparison between the use of goserelin or oophorectomy.

2b. Goserelin 3.6 mg compared to oophorectomy or irradiation of the ovaries as adjuvant therapy.

An oophorectomy can be offered to peri or premenopausal women with hormone dependent EBC as an alternative to adjuvant chemotherapy or the use of a LHRH analogue.

An indirect comparison between goserelin 3.6 mg and ovarian ablation as initial adjuvant treatments can be constructed using historical data comparing ovarian ablation to no systemic adjuvant treatment (chemotherapy or hormonal therapy) and from patients in the Cuzick meta-analysis who were randomised to LHRH agonists or no systemic adjuvant therapy.

Historical comparison of oophorectomy versus no systemic treatment

Nine studies were included in the Oxford clinical trials group meta-analysis of the data from ovarian ablation published in 1996. Five of the studies involved ablation of ovarian function by irradiation and four studies involved surgical removal of the ovaries. All studies were conducted in the absence of chemotherapy and the control group for the studies was no adjuvant therapy. A total of 1169 women were less than 50 years old in these studies.

The effect of ovarian ablation in the absence of chemotherapy is a 25 % reduction in the rate of recurrence (standard deviation +- 7 %, p=0.0005) compared to no adjuvant treatment. The reduction in the rate of death between patients randomised to ovarian ablation or no adjuvant therapy is similar at 24 % (standard deviation +-7 %, p=0.0006).

Comparison of LHRH agonist and no systemic therapy

The Cuzick et al meta-analysis contained data from five trials comparing goserelin to no other adjuvant treatment, with 167 patients randomised to the goserelin arm and 171 patient randomised to the control arm. The reduction in recurrence of breast cancer was 28 % (95 % CI -50.5% to 3.5 %, p=0.08) and the reduction in deaths following recurrence was 17.8 5 (95 % CI -52.8 to 42.9 %, p=0.11).

Indirect comparison
For comparative purposes, an indirect comparison was constructed between the Early Breast Cancer Trialists' Collaboration meta-analysis of oophorectomy data compared to no systemic adjuvant treatment and the Cuzick et al meta-analysis data of the use of goserelin 3.6 mg compared to no systemic adjuvant. The submission stated that the treatment effects appear similar.

The authors of the LHRH agonist meta-analysis paper (Cuzick et al) state that whilst the reduction in risk with goserelin treatment was not significant it was similar to earlier trials of ovarian ablation as adjuvant therapy. The wide confidence intervals are likely to be attributed to the smaller patient numbers in the goserelin 3.6 mg versus no adjuvant chemotherapy trials.

For PBAC comments, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that:
(1) goserelin 3.6 mg is equally as efficacious as combination chemotherapy, but has a superior safety profile and is associated with a better quality of life, and
(2) goserelin 3.6 mg is equally efficacious as an oophorectomy as adjuvant treatment.

The PBAC noted the significant advantage of goserelin for some women in that it avoided the need to cope with infertility contemporaneously with a diagnosis of breast cancer.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-analysis for goserelin as an alternative to chemotherapy, and a cost minimisation analysis for goserelin as an alternative to oophorectomy.

The PBAC noted that the main translational issue was that the majority of the clinical data compares goserelin to the chemotherapy regimen CMF, which is no longer used in clinical practice. A further translational issue related to the duration of goserelin therapy in clinical practice in each of the settings identified above.

Goserelin as an alternative to chemotherapy

The submission estimated that goserelin produces a cost saving per patient when offered as an alternative to chemotherapy.

Goserelin as an alternative to oophorectomy

The submission estimated that goserelin is associated with a nominal incremental cost when offered as an alternative to surgical oophorectomy.

Goserelin in EBC

The submission stated that the results of the cost analysis across both treatment settings indicate an estimated marginal cost saving.

11. Estimated PBS Usage and Financial Implications

As optimum duration of treatment in either clinical setting has not been established, for the purposes of the submission patients were assumed to receive between one to two years treatment with goserelin as an alternative to chemotherapy, and as an alternative to oophorectomy it was assumed 90% of patients were treated for up to three years with goserelin with the remaining 10% of patients receiving treatment with goserelin for four to five years. These estimates were based on expert opinion from the Medical Oncology Group of Australia and the National Breast and Ovarian Cancer Centre.

The submission estimated the total number of patients treated with goserelin per year as an alternative to chemotherapy and oophorectomy would be less than 10,000.

The overall net cost to the PBS in Year 5 of listing goserelin for EBC was estimated to be less than $10 million. The estimated net savings to the MBS and overall net savings to government in Year 5 was less than $10 million, respectively.

12. Recommendation and Reasons

The PBAC recommended listing goserelin on the PBS for hormone dependent breast cancer as an alternative to adjuvant chemotherapy in peri or pre-menopausal women on the basis of clinical need and acceptable cost-effectiveness. The PBAC deferred the recommendation for listing goserelin for treatment after adjuvant chemotherapy pending provision of further data in that patient population.

The PBAC acknowledged there was a clinical need for goserelin in pre-menopausal women with breast cancer who wished to preserve their fertility and avoid chemotherapy. The PBAC noted that adjuvant chemotherapy risks for some patients. The PBAC considered that there is a well defined subgroup of breast cancer patients who would be suitable for goserelin who are mainly node negative, have small tumours and are usually between 35 and 40 years of age.

The PBAC noted that the scientific basis for assessing efficacy was from three sources: Cuzick et al, Lancet 2007, Cochrane Review, 2008 Sharma R and Oxford Early Breast Cancer Trialists' Collaboration, Lancet 1996 which were all historical trials. The PBAC noted the Cuzick et al (2007) meta-analysis which showed that LHRH analogues were equally as efficacious as chemotherapy (CMF) in preventing recurrence of breast cancer (HR 1.04, 95% CI 0.92-1.17, p=0.52) and preventing death after recurrence of breast cancer (HR 0.93, 95% CI 0.79-1.10, p= 0.40). The Cochrane Review showed superior acute safety profile to chemotherapy and improvements in quality of life in first 6 months compared with chemotherapy then no difference beyond the first year. After 2 years treatment with goserelin the quality of life may be worse than for those patients who had adjuvant chemotherapy for an initial three months and this is reflected in clinical practice where use of goserelin declines markedly over 2 years, according to expert opinion in the submission.

The PBAC noted that there are no direct comparative data on safety or quality of life. However, simple comparisons and expert opinion support the conclusion that goserelin is safe and better tolerated than chemotherapy or permanent and premature ovarian failure. The PBAC also noted the significant advantage of goserelin for some women in that it avoided the need to cope with infertility contemporaneously with a diagnosis of breast cancer.

The PBAC noted that the estimated usage of goserelin as an alternative to chemotherapy was low and would result in a cost-saving to the Government. However, listing for treatment after adjuvant chemotherapy would be at a small additional cost per patient to the Government. The PBAC considered that the appropriate comparator in this setting was tamoxifen which was cheaper and that a comparison versus tamoxifen would be more appropriate for this population.

Recommendation:
GOSERELIN ACETATE, subcutaneous implant, 3.6 mg (base) in pre-filled injection syringe

Add the following indication to the current restriction:

Restriction: <u>Authority required</u>
Hormone-dependent breast cancer as an alternative to adjuvant chemotherapy in peri or pre-menopausal women;

13. 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.

14. Sponsor's Comment

AstraZeneca Australia thanks the PBAC for recommending the use of goserelin as an alternative to chemotherapy for women with early breast cancer. We would also like to thank the Medical Oncology Group of Australia for its help and support in the initiation and compilation of this PBAC submission.