Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Leuprorelin acetate in addition to tamoxifen or an aromatase inhibitor for ER-positive early stage breast cancer in premenopausal women - adjuvant

NIHRIO ID	24224	**NICE ID**	10018
Developer/Company	Takeda UK Ltd	**UKPS ID**	649635

SUMMARY

Leuprorelin acetate in addition to tamoxifen or an aromatase inhibitor is in clinical development as an adjuvant treatment of ER-positive early stage breast cancer in premenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). Breast cancer is the most common female cancer in the UK. In early stage breast cancer the tumour has not spread to any other parts of the body, and the patient will have surgery to remove the tumour. Following surgery, adjuvant therapy (hormone or chemotherapy) is given to women with ER-positive cancer for 5 years or longer, to improve the success of the treatment.

One of the most common hormone therapies given to premenopausal women is tamoxifen, which blocks the oestrogen receptors, stopping oestrogen from telling the cancer cells to grow. Leuprorelin acetate works by preventing the ovaries producing oestrogen. A similar drug currently commonly used is goserelin, which is given as an injection every 4 weeks. If licensed, leuprorelin acetate will offer another treatment option for premenopausal women with early stage breast cancer.

PROPOSED INDICATION

Oestrogen-positive (ER-positive) early stage breast cancer in premenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement) - adjuvant[a]

TECHNOLOGY

DESCRIPTION

Leuprorelin acetate (Prostap DCS) is a gonadotropin-releasing hormone (GnRH) analogue. It is a synthetic nonapeptide analogue of naturally occurring GnRH. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. It has potent luteinising hormone releasing hormone (LHRH) agonist properties when given during short-term and intermittent therapy, however, when administered in a continuous, nonpulsatile manner, LHRH analogues induce inhibition of gonadotropin secretion. Upon binding to pituitary LHRH receptors, leuprorelin acetate produces an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to an acute rise in levels of testosterone and dihydrotestosterone. However, within five to eight days after drug administration, LHRH analogues produce desensitisation of the LHRH receptor complex and/or downregulation of the anterior pituitary gland. Due to the fact that there are fewer receptors on the cell surface, cellular stimulation is decreased, and less gonadotropin is synthesised and secreted. Eventually, after several weeks of LHRH agonist therapy, LH and FSH secretion is suppressed. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian steroid secretion. This effect is reversible on discontinuation of therapy.[1,2]

Leuprorelin acetate (Prostap DCS) in combination with tamoxifen or an aromatase inhibitor is in clinical development as an adjuvant treatment of ER-positive early stage breast cancer in premenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement).[b]

INNOVATION AND/OR ADVANTAGES

Ovarian function suppression (OFS) in addition to endocrine therapy is recommended by the National Institute for Heath and Care Excellence (NICE) as a treatment option for premenopausal women with ER-positive invasive breast cancer as an alternative to chemotherapy.[3,4] There is evidence that OFS increased overall survival when combined with tamoxifen, and that women who have had chemotherapy benefited more.[3]

The GnRH analogue goserelin (Zoladex 3.6mg implant) is currently licensed in the UK for ER-positive early breast cancer, and is administered as a SC injection administered into the anterior abdominal wall every 28 days.[5] Triptorelin (Decapeptyl SR 3mg) is also licensed in the UK as adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy, and is administered as an intramuscular injection every 4 weeks.[6]

[a] Information provided by company on UK PharmaScan
[b] Information provided by company on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Leuprorelin acetate (Prostap SR DCS, Prostap 3 DCS) is currently licensed in the UK for the following indications:[7,8]

- Metastatic prostate cancer
- Locally advanced prostate cancer as an alternative to surgical castration
- As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- Management of endometriosis, including pain relief and reduction of endometriotic lesions
- In children – treatment of central precocious puberty (girls under 9 years of age, boys under 10 years of age)

Leuprorelin acetate (Prostap SR DCS) is currently licensed in the UK for the following additional indications:[7]

- Endometrial preparation prior to intrauterine surgical procedures including endometrial ablation or resection
- Preoperative management of uterine fibroids to reduce their size and associated bleeding

In women, adverse effects occurring most frequently (≥1/10 to ≥1/100 to <1/10) with leuprorelin acetate are associated with hypo-oestrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness.[7,8]

Leuprorelin acetate is also at pre-registration stage for:

- the preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy[9]
- adjuvant treatment in advanced breast cancer suitable for hormonal manipulation in pre- and perimenopausal women[10]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer most commonly starts in the cells that line the ducts of the breast.[11] There are several types of breast cancer described according to the receptors expressed on the surface of tumour cells, stage of diagnosis, and rate of growth.[12] Breast cancer that has receptors for the hormone oestrogen (which is found naturally in the body) is known as oestrogen receptor positive (ER-positive) cancer.[13]

The causes of breast cancer are not completely understood, however a number of factors are known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, being taller, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors. The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).[14]

Symptoms of breast cancer may include breast lump, change in size, shape or feel of the breast, breast pain, skin changes including puckering, dimpling, a rash, or redness of the skin of the breast, change in the position of the nipple, and fluid leaking from the nipple. Sometimes, in a rare type of breast cancer the whole breast might look red and inflamed and feel sore.[15]

Stages of breast cancer tells how big it is and whether it has spread.[16] The number staging system for breast cancer divides breast cancers into 4 stages, from 1 to 4. Stage 1 is the earliest stage and stage 4 means the cancer has spread to another part of the body.[17] Stages 1 and 2 are also called early breast cancer.[18,19]

Breast cancer patients experience physical symptoms and psychosocial distress that adversely affect their quality of life (QOL). Treatment, including chemotherapy, can cause physical and psychological problems that adversely affect patient QOL, and cancer can have other effects including anger, grief, suffering and pain.[20]

CLINICAL NEED AND BURDEN OF DISEASE

The directly age-standardised incidence rate of breast cancer in females in England in 2016 was 167.9 per 100,000.[21] Incidence rates are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[22]

Breast cancer incidence is strongly related to age, with the highest incidence rates being in older people. In England in 2016 there were 45,656 registrations of newly-diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), of which 13,951 (31%) were for younger women (aged 15 to 54 years).[21]

The majority (80%) of breast cancers are diagnosed at an early stage (36,508 cases in England in 2016 were diagnosed at Stage 1 or Stage 2).[23] It is not possible to give a breakdown of cases by age and stage.

For women diagnosed with breast cancer in England in 2011-2015, predicted estimates of 5-year and 10-year net survival are 87.5% and 81.1% for women aged 15-44 years, and 91.7% and 87.3% for women aged 45-54 years.[24]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

NICE recommends:[3]

- Surgery: treat people with invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery
- Neoadjuvant chemotherapy: consider this for people with ER-positive invasive breast cancer as an option to reduce tumour size if chemotherapy is indicated. Advise premenopausal women that neoadjuvant chemotherapy may be more likely to produce a clinical response than neoadjuvant endocrine therapy, but that some tumours do respond to neoadjuvant endocrine therapy
- Adjuvant therapy: consider this after surgery for people with invasive breast cancer. Use the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy. When using version 2.0 of the tool be aware that it is less accurate for women under 30 with ER-positive breast cancer, women with tumours larger than 50mm, and the validation may have under-represented some ethnic groups. Adjuvant therapies recommended for premenopausal women include endocrine therapy, chemotherapy

CURRENT TREATMENT OPTIONS

The following are recommended by NICE as adjuvant therapy for premenopausal women with early and locally advanced ER-positive invasive breast cancer:[3]

- Endocrine therapy:
  - Offer tamoxifen as the initial adjuvant endocrine therapy
  - Consider ovarian function suppression in addition to endocrine therapy
  - Consider extending the duration of tamoxifen therapy for longer than 5 years

- Chemotherapy:
  - For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline

- Radiotherapy:
  - Offer whole-breast radiotherapy to women who have had breast-conserving surgery with clear margins
  - Offer adjuvant post-mastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins
  - Use external beam radiotherapy giving 40Gy in 15 fractions as standard practice after breast-conserving surgery or mastectomy
  - Offer an external beam boost to the tumour bed for women with a high risk of local recurrence, following whole-breast radiotherapy
  - Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 4 or more involved axillary lymph nodes
  - Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 1 to 3 positive lymph nodes if they have other poor prognostic factors and good performance status
  - Consider including the internal mammary chain within the nodal radiotherapy target for people with node-positive (macrometastases) invasive breast cancer
  - The Intrabeam radiotherapy system is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour[25]
  - Use of the Intrabeam radiotherapy system is recommended only using machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements[25]

PLACE OF TECHNOLOGY

If licensed, leuprorelin acetate will offer an additional adjuvant treatment option for ER-positive early stage breast cancer in premenopausal women at higher risk of disease recurrence.

CLINICAL TRIAL INFORMATION

Trial	SOFT, NCT00066690, IBCSG 24-02; tamoxifen or exemestane in addition to ovarian function suppression (OFS) vs tamoxifen; phase III
Sponsor	International Breast Cancer Study Group
Status	Ongoing, published
Source of Information	Publication[26,27,28], trial registry[29]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled

Participants	n=3,066; aged 18-65 yrs; premenopausal females; breast cancer; hormone-responsive; adjuvant therapy after surgery
Schedule	Randomised to: • Experimental Arm 1: tamoxifen 20mg orally daily plus OFS (triptorelin 3.75mg by intramuscular (IM) injection every 4 wks or surgical oophorectomy or ovarian irradiation) for 5 yrs • Experimental Arm 2: exemestane 25mg orally daily plus OFS (triptorelin 3.75mg by IM injection every 4 wks or surgical oophorectomy or ovarian irradiation) for 5 yrs • Active comparator: tamoxifen 20mg orally daily for 5 yrs
Follow-up	Active treatment for 5 yrs, follow-up every 3 mths for 1 yr, every 6 mths for 5 yrs, and annually thereafter. Quality of life assessed at baseline, every 6 mths for 2 yrs, and then annually for 4 yrs.
Primary Outcomes	Disease-free survival
Secondary Outcomes	• Breast cancer-free interval • Distant recurrence-free interval • Overall survival • Quality of life
Key Results	SOFT trial: After a median follow-up of 67 months, the estimated disease-free survival rate at 5 years was 86.6% in the tamoxifen-OFS group and 84.7% in the tamoxifen group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.83; 95% confidence interval [CI], 0.66 to 1.04; P=0.10). Multivariable allowance for prognostic factors suggested a greater treatment effect with tamoxifen plus OFS than with tamoxifen alone (hazard ratio, 0.78; 95% CI, 0.62 to 0.98). Most recurrences occurred in patients who had received prior chemotherapy, among whom the rate of freedom from breast cancer at 5 years was 82.5% in the tamoxifen-OFS group and 78.0% in the tamoxifen group (hazard ratio for recurrence, 0.78; 95% CI, 0.60 to 1.02). At 5 years, the rate of freedom from breast cancer was 85.7% in the exemestane-OFS group (hazard ratio for recurrence vs. tamoxifen, 0.65; 95% CI, 0.49 to 0.87). SOFT and TEXT trials latest results (2018): In SOFT, the 8-year disease-free survival rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus OFS, and 85.9% with exemestane plus OFS (P=0.009 for tamoxifen alone vs. tamoxifen plus OFS). The 8-year rate of overall survival was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus OFS, and 92.1% with exemestane plus OFS (P=0.01 for tamoxifen alone vs. tamoxifen plus OFS); among the women who remained premenopausal after chemotherapy, the rates were 85.1%, 89.4%, and 87.2%, respectively. Among the women with cancers that were negative for HER2 who received chemotherapy, the 8-year rate of distant recurrence with exemestane plus OFS was lower than the rate with tamoxifen plus OFS (by 7.0 percentage points in SOFT and by 5.0 percentage points in TEXT). Among premenopausal women with breast cancer, the addition of OFS to tamoxifen resulted in significantly higher 8-year rates of both disease-free and overall survival than tamoxifen alone. The use of exemestane plus OFS resulted in even higher rates of freedom from recurrence.
Adverse effects (AEs)	SOFT and TEXT trials latest results (2018): The frequency of adverse events was higher in the two groups that received OFS than in the tamoxifen-alone group.

	Targeted adverse events of grade 3 or higher were reported in 24.6% of the tamoxifen group in SOFT, 31.0% of the combined tamoxifen-OFS group, and 32.3% of the combined exemestane-OFS group. Thrombosis or embolism of any grade was reported in 2.2% of the patients in the tamoxifen-only group, in 2.3% of those in the tamoxifen-OFS group, and in 1.2% of those in the exemestane-OFS group. Musculoskeletal symptoms of grade 3 or 4 occurred in 6.7% of the patients in the tamoxifen group, in 5.7% of those in the combined tamoxifen-OFS group, and in 11.4% of those in the combined exemestane-OFS group. Osteoporosis (defined as a T score of less than −2.5, which corresponds to a grade 2, 3, or 4 adverse event) was reported in 3.9% of the patients in the tamoxifen group, in 7.2% of those in the combined tamoxifen-OFS group, and in 14.8% of those in the combined exemestane-OFS group. Vaginal dryness and dyspareunia were most frequent in the exemestane-OFS group. Hypertension and glucose problems were more frequent in the two OFS groups than in the tamoxifen-only group.

Trial	TEXT, NCT00066703, IBCSG 25-02; tamoxifen or exemestane in addition to OFS; phase III
Sponsor	International Breast Cancer Study Group
Status	Ongoing, published
Source of Information	Publication[26,28] , trial registry[30]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=2,672; aged 18-65 yrs; premenopausal females; breast cancer; hormone-responsive; adjuvant therapy after surgery
Schedule	Randomised to: • Experimental Arm: exemestane 25mg orally daily plus OFS (triptorelin 3.75mg by IM injection every 4 wks) for 5 yrs. Exemestane begins after the completion of adjuvant chemotherapy if given, or approx. 6-8 wks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation allowed after at least 6 mths of triptorelin. • Active comparator: tamoxifen 20mg orally daily plus OFS (triptorelin 3.75mg by intramuscular (IM) injection every 4 wks) for 5 yrs. Tamoxifen begins after the completion of adjuvant chemotherapy if given, or approx. 6-8 wks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation allowed after at least 6 mths of triptorelin.
Follow-up	Active treatment for 5 yrs, follow-up every 3 mths for 1 yr, every 6 mths for 5 yrs, and annually thereafter. Quality of life assessed at baseline, every 6 mths for 2 yrs, and then annually for 3 yrs.
Primary Outcomes	Disease-free survival
Secondary Outcomes	• Breast cancer-free interval • Distant recurrence-free interval • Overall survival • Quality of life
Key Results	See table above
Adverse effects (AEs)	See table above

Trial	TABLE; leuprorelin acetate 3-monthly formulation (LAD-3M) vs cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy; phase III
Sponsor	Takeda Ltd
Status	Published
Source of Information	Publication[31]
Location	EU (not UK)
Design	Randomised, active-controlled
Participants	n=599; premenopausal females; breast cancer; stage 2 or 3a, ER-positive; adjuvant therapy within 6 wks of definite surgery
Schedule	Randomised to : • Experimental Arm: LAD-3M 11.25mg as subcutaneous injection every 3 mths for 2 yrs • Active comparator: CMF chemotherapy in 4-wk intervals for 6 courses. A cycle of CMF consisted of cyclophosphamide (500 mg/m^2, IV infusion on days 1 and 8), methotrexate (40 mg/m^2 IV infusion on days 1 and 8), and fluorouracil (600 mg/m^2, IV infusion on days 1 and 8)
Follow-up	• Active treatment for 2 yrs (LAD-3M, 6 mths for CMF chemotherapy. Follow-up every 3 mths for 2 yrs, every 6 mths thereafter.
Primary Outcomes	Recurrence-free survival
Secondary Outcomes	• Overall survival • Adverse events • Oestrogen suppression • Menstrual status • Subjective state of health
Key Results	With a median follow-up of 5.8 years, recurrence-free survival was similar for patients treated with LAD-3M or CMF (hazard ratio [HR], 1.19; 95% CI, 0.94 to 1.51; P = .15). There was no substantial heterogeneity in the relative treatment effect among subgroups defined by age, progesterone receptor (PR) status, nodal status, hormone levels, or menstrual recovery after treatment. Exploratory overall survival analysis favoured LAD-3M (HR, 1.50; 95% CI, 1.13 to 1.99; P = .005). Conclusion: the 3-monthly depot LHRH-agonist leuprorelin acetate is an effective adjuvant treatment in premenopausal patients with hormone receptor–positive, node-positive breast cancer that is not inferior to CMF.
Adverse effects (AEs)	Chemotherapy-related adverse effects such as nausea, vomiting, and alopecia were more common with CMF, whereas symptoms of oestrogen suppression such as hot flushes and sweating were initially more pronounced with LAD-3M.

Trial	ABC, NCT00002582; leuprorelin acetate 3-monthly formulation (LAD-3M) vs cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy; phase III
Sponsor	Institute of Cancer Research, United Kingdom
Status	Published

Source of Information	Publication[32], trial registry[33]
Location	UK
Design	Randomised, active-controlled
Participants	n=2,144; pre- or perimenopausal females; breast cancer; early stage; adjuvant therapy after surgery
Schedule	Randomised to Arm 1: Tamoxifen 20mg daily for 5 yrs plus CMF monthly for 6 courses, or doxorubicin/cyclophosphamide (AC) every 3 wks for 4 courses Arm 2: Tamoxifen 20mg daily for 5 yrs plus OFS by oophorectomy, radiation castration, or leuprolide or goserelin Arm 3: Tamoxifen 20mg daily for 5 yrs plus OFS plus chemotherapy with CMF or AC Active comparator: Tamoxifen 20mg daily for 5 yrs
Follow-up	Annual follow-up
Primary Outcomes	Overall survival
Secondary Outcomes	• Breast cancer-specific mortality • Relapse-free survival
Key Results	Between 1993 and 2000, 2,144 (1,063 ovarian ablation or suppression, 1,081 no ovarian ablation or suppression) patients were randomly assigned. A total of 942 (89%) received ovarian ablation or suppression as allocated. Overall, no evidence of a benefit for ovarian ablation or suppression was observed for relapse-free survival (relapse in the ovarian ablation/suppression versus no ovarian ablation/suppression group, 290 events versus 306 events, HR = 0.95, 95% confidence interval [CI] = 0.81 to 1.12; P = .56) or overall survival (death from any cause in the ovarian ablation or suppression versus no ovarian ablation/suppression group, 215 events versus 230 events, HR = 0.94, 95% CI = 0.78 to 1.13; P = .44), nor were differences seen after adjustment for age, nodal status, or oestrogen receptor (ER) status.
Adverse effects (AEs)	No individual adverse event data was recorded because the toxicity profile of trial treatments was considered to be well characterized

ESTIMATED COST

Leuprorelin acetate (Prostap SR DCS) is already marketed in the UK; 1 x 3.75mg powder and solvent for suspension for injection pre-filled syringe has a NHS indicative price of £75.24. Leuprorelin acetate (Prostap 3 DCS) is additionally marketed in the UK; 1 x 11.25mg powder and solvent for suspension for injection pre-filled syringe has a NHS indicative price of £225.72.[34]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer (TA501). January 2018
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018
- NICE quality standard. Breast cancer (QS12). September 2011, updated June 2016
- NICE cancer service guideline. Improving outcomes in breast cancer (CSG1). August 2002

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. Clinical Commissioning Policy: Radiotherapy after primary surgery for breast cancer. 16038/P

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[35]
- Scottish Intercollegiate Guidelines Network (SIGN). Treatment of primary breast cancer (SIGN 134). 2013.[36]

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