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Leuprorelin acetate for advanced breast cancer in pre or perimenopausal women – adjuvant

NIHRIO ID	24228	**NICE ID**	10019
Developer/Company	Takeda UK Ltd	**UKPS ID**	649665

SUMMARY

Leuprorelin acetate is being developed as an adjuvant treatment given by subcutaneous injection for pre and perimenopausal women with advanced breast cancer suitable for hormonal manipulation. Breast cancer is the most common female cancer in the UK. Breast cancers that are stimulated to grow by the hormones oestrogen or progesterone are known as hormone receptor-positive cancers. Advanced breast cancer is when the cancer has spread to other parts of the body. Treatments at this stage are not curative and will aim to reduce the progression of the cancer and metastases. Eligible patients may have surgery which is usually followed by adjuvant therapy (hormone or chemotherapy) to improve the success of the treatment.

Leuprorelin is a gonadotropin-releasing hormone (GnRH) analogue, when given chronically will block the production of oestrogen and progesterone hormones from the ovaries. A similar drug currently commonly used is goserelin, which is given as an injection every 4 weeks. If licensed, leuprorelin acetate will offer an additional adjuvant treatment option for pre and perimenopausal women with advanced breast cancer that is suitable for hormonal manipulation.

PROPOSED INDICATION

As adjuvant treatment in pre- and perimenopausal women with advanced breast cancer suitable for hormonal manipulation.[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 is being developed as an adjuvant treatment given by subcutaneous injection for women with pre and perimenopausal advanced breast cancer suitable for hormonal manipulation. Proposed dose is 3.75mg every calendar month or 11.25mg every three calendar months.[a, b]

INNOVATION AND/OR ADVANTAGES

Ovarian function suppression in addition to endocrine therapy is recommended by the National Institute for Heath and Care Excellence (NICE) as a treatment option for or premenopausal women with oestrogen receptor (ER)-positive invasive breast cancer.[3] The GnRH analogue, goserelin (Zoladex) is currently licensed in the UK for advanced breast cancer in pre and perimenopausal women suitable for hormonal manipulation. Its pharmaceutical form is implant in pre-filled syringes administered every 28 days.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Leuprorelin acetate (Prostap SR DCS, Prostap 3 DCS) is currently licensed in the UK for the following indications:[6,7]

- 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

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

- 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)
- 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-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness.[6,7]

Leuprorelin acetate in combination with tamoxifen or an aromatase inhibitor is currently at pre-registration stage of development as an adjuvant treatment in early stage oestrogen receptor (ER) positive breast cancer for premenopausal women at higher risk of disease recurrence.[8]

Leuprorelin acetate is also currently at pre-registration stage of development for the preservation of ovarian function in premenopausal women with neoplastic disease undergoing chemotherapy.[9]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer most commonly starts in the cells that line the ducts of the breast. [10] 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.[11] Breast cancers that are stimulated to grow by the hormones oestrogen or progesterone, which are found naturally in the body are known as hormone receptor-positive cancers.[12]

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).[13]

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.[14]

Stages of breast cancer tells how big it is and whether it has spread. 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. [15,16] Stage 4 is also called advanced cancer, or metastatic breast cancer.[17]

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.[18]

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.[19] 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).[20]

Breast cancer incidence is strongly related to age, with the highest incidence rates being in older people.[21] In England in 2016 there were 13,951 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50) for younger women (in females aged between 15 to ≤ 54 years).[22]

Proportion of breast cancer diagnosed at stage 4 in England in 2016 was 8.5%.[23] Using the data from registrations of newly diagnosed cases of breast cancer for females aged 15 to ≤ 54 years in England in 2016, this would be equivalent to 1,186 breast cancer cases diagnosed at stage 4.[22] The majority of patients (75%) diagnosed with metastatic breast cancer are hormone receptor (HR) positive[24] (suitable for hormonal manipulation) which would be equivalent to 890 of the newly diagnosed cases at stage 4 in England in 2016.[22]

Age standardised mortality rate of breast cancer in females in the UK for 2016 was 34.1 per 100,000.[25] In England in 2017, there were 1,619 registrations of death from neoplasm of the breast in females aged 15 to ≤ 54 years.[26]

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.[27]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Advanced breast cancer patients receive information and support on the therapies available to them. Treatments at this stage are not curative and will aim to reduce the progression of the cancer and metastases. The approach to treatment is likely to be multidisciplinary and involve different types of clinicians including oncologists, radiologists and radiotherapists.[3, 12, 28]

The presence and extent of visceral and bone metastases should be assessed using imaging technologies such as radiography, ultrasound, computed tomography (CT) scans, magnetic resonance imaging (MRI) and/or bone scintigraphy. Also risk for bone fractures in the proximal limbs due to bone metastases need to be assessed using bone scintigraphy and/or plain radiography.[3, 28]
People with newly diagnosed invasive breast cancer have the ER and human epidermal growth factor receptor 2 (HER2) status of the tumour assessed to classify the primary tumour and decide how best to treat and manage the cancer. Recurrent tumours (either at the site of the primary tumour or metastatic tumours) should be assessed for their ER and HER2 status, if a change in receptor status will lead to a change in management.[29]

Systemic disease-modifying therapy for advanced breast cancer include endocrine therapy such as aromatase inhibitor, tamoxifen and ovarian suppression; one drug or a combination of 2 or 3 chemotherapy drugs such as docetaxel, vinorelbine or capecitabine, and gemcitabine; and biological therapy. Patients also should be provided with supportive care and management of complications.[3, 30]

CURRENT TREATMENT OPTIONS

- Tamoxifen and ovarian suppression are recommended by NICE as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.[3]
- Ovarian suppression is recommended by NICE for the treatment of premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.[3]
- Goserelin is currently used as a treatment option for ovarian suppression.[12] Goserelin is indicated for advanced breast cancer in pre and perimenopausal women suitable for hormonal manipulation.[4]

PLACE OF TECHNOLOGY

If licensed, leuprorelin acetate will offer an additional adjuvant treatment option for pre and perimenopausal women with advanced breast cancer suitable for hormonal manipulation.

CLINICAL TRIAL INFORMATION

The company has provided two journal articles of studies conducted in the past that investigated the effect of LHRH agonist in combination with tamoxifen versus tamoxifen alone. In the study by Jonat et al. 1995,[31] goserelin with or without tamoxifen was administered in 318 pre- and perimenopausal advanced breast cancer patients. With a median follow-up of 93 weeks, 31% of goserelin-treated patients had objective responses (UICC criteria) compared with 38% of goserelin plus tamoxifen-treated patients (P = 0.24). There was a modest benefit in favour of combination therapy in time to progression (P = 0.03) but not in survival (P = 0.25). Median follow-up for survival was 117.5 weeks. Median times for disease progression and survival were 23 and 127 weeks in the goserelin alone group and 28 and 140 weeks in the combination group, respectively. In 115 patients with skeletal metastases only, significant differences in favour of combination therapy were seen in response rate, time to progression and survival. Both treatments were well tolerated and no additional safety issues were associated with combination therapy.[31]

In the study by Klijn et al. 2001, [32] a meta-analysis of four clinical trials that compared the effect of tamoxifen and (LHRH) agonist versus (LHRH) agonist alone in a total of 506 premenopausal women with advanced breast cancer was reported. With a median follow-up of 6.8 years, there was a significant survival benefit (stratified log-rank test, P = .02; hazards ratio [HR] = 0.78) and progression-free survival benefit (stratified log-rank test, P = .0003; HR = 0.70) in favour of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment (stratified Mantel Haenszel test, P = .03; odds ratio = 0.67).[32]

ESTIMATED COST

Leuprorelin acetate is already marketed in the UK. A pre-filled disposable injection (POM) of Prostap SR DCS 3.75mg powder and solvent for suspension for injection costs £75.24 and A pre-filled disposable injection (POM) of Prostap 3 DCS 11.25mg powder and solvent for suspension for injection costs £225.72.[33]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Ribociclib in combination with endocrine therapy and goserelin for previously untreated hormone receptor-positive, HER2-negative advanced breast cancer in premenopausal women (ID1307). Expected publication date to be confirmed.
- NICE clinical guidance. Advanced breast cancer: diagnosis and treatment (CG81). February 2009. Updated August 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. March 2018.[34]
- European School of Oncology (ESO) and European Society for Medical Oncology (ESMO). ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). 2014.[35]

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