

**NIHR Innovation Observatory
Evidence Briefing: May 2018****Triptorelin pamoate (subcutaneous injection) for
prostate cancer**

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LAY SUMMARY

Prostate cancer is cancer of the prostate gland (a small organ in a man's pelvis) and is the second most common cancer in the UK. There are three stages: localised, locally-advanced and advanced (or metastatic) prostate cancer. The symptoms of prostate cancer may vary depending on the stage of cancer but can include pain, tiredness, problems emptying the bladder and the bowels. About half of men diagnosed with locally-advanced prostate cancer will see their cancer spread to other body organs (i.e. becoming metastatic).

Triptorelin is being developed as an injection under the skin (subcutaneous) for the treatment of locally advanced or metastatic prostate cancer. It is already marketed for this condition but is given by injection deep into the muscles (intramuscular). Triptorelin is an artificial analogue of natural gonadotropin-releasing hormone that acts to slowly reduce the level of testosterone in the body. The first administration of triptorelin stimulates an increase in testosterone levels but prolonged administration leads to a fall in plasma testosterone or oestradiol to castrate levels which is maintained for as long as the product is administered. Triptorelin as a subcutaneous injection formulation has the potential advantage of improved safety and local tolerability when compared to intramuscular injection formulation.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Locally advanced or metastatic prostate cancer (adjuvant/neoadjuvant prior to radiotherapy/adjuvant to radical prostatectomy)

TECHNOLOGY

DESCRIPTION

Triptorelin is a synthetic decapeptide analogue of natural gonadotropin-releasing hormone.¹ The first administration of triptorelin stimulates the release of pituitary gonadotropins with a transient increase in testosterone levels (“flare-up”) in men. Prolonged administration leads to a suppression of gonadotropins and a fall in plasma testosterone or oestradiol to castrate levels after approximately 20 days, which is maintained for as long as the product is administered.²

In the phase III trial (NCT01715129), 11.25mg of triptorelin pamoate was given subcutaneously on day 1 and day 92 to patients with locally advanced or metastatic prostate cancer.³

Triptorelin is currently licensed as an intramuscular injection for the treatment of the following conditions:¹

- Locally advanced, non-metastatic prostate cancer as an alternative to surgical castration
- Metastatic prostate cancer
- Endometriosis
- Precocious puberty (onset before 8 years in girls and 10 years in boys)

In the adjuvant setting, triptorelin is licensed for the treatment of patients with high-risk localised or locally advanced prostate cancer after radiotherapy and for patients with locally advanced prostate cancer at high risk of disease progression following radical prostatectomy.¹ Triptorelin is also licensed in the neoadjuvant setting prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.¹

Common adverse effects in men include decreased libido, lower limb paresthesia, hot flush, hyperhidrosis, back pain, erectile dysfunction and asthenia. Common adverse effects in women include decreased libido, mood disorder, sleep disorder, headache, acne, hyperhidrosis, seborrhea, breast disorder, dyspareunia, genital bleeding, ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, vulvovaginal dryness and asthenia.¹

Triptorelin is in phase II and phase III trials for indications such as advanced prostate cancer and precocious puberty.⁴

INNOVATION and/or ADVANTAGES

Triptorelin is already licensed for locally advanced or metastatic prostate cancer in the adjuvant/neoadjuvant setting prior to radiotherapy and also in the adjuvant to radical prostatectomy setting. However, the route of administration is via intramuscular injection.

The development of triptorelin as a subcutaneous injection formulation has the potential advantage of improved safety and local tolerability when compared to intramuscular injection formulation.

DEVELOPER

Ipsen Ltd

PATIENT GROUP

BACKGROUND

Prostate cancer is the most common cancer in men in the UK (not counting non melanoma skin cancer).⁵ It affects the prostate gland which is a small gland in the pelvis found only in men. It is located between the penis and the bladder and surrounds the urethra. The main function of the prostate is to help in the production of semen.⁶ The cancer starts in the glandular cells in the prostate and are known as acinar adenocarcinomas. It is more common in black Caribbean and black African men than in white men, and is very rare in Asian men. More than half the men (50%) diagnosed with prostate cancer in the UK each year are aged 70 and over.⁷

Early prostate cancer often has no symptoms at all. When symptoms occur, these include increased urinary frequency, nocturia, urinary hesitancy, urgency, post-void dribbling, blood in urine or semen, erectile dysfunction (uncommon) and poor stream.^{6,8} Symptoms that the cancer may have spread include bone and back pain, a loss of appetite, pain in the testicles and unexplained weight loss.⁶ Although the cause of prostate cancer is not known, a number of risk factors have been identified which include (increased) age, ethnicity, family history, obesity, lack of exercise, high calcium diet, being taller, high levels of insulin like growth factor (IGF-1), having had a previous cancer, vasectomy, prostatitis and being exposed to cadmium and cadmium compounds.^{5,6}

Prostate cancer can be divided into localised (confined to the prostate gland), locally advanced (spread outside the capsule of the prostate gland) and advanced cancer (spread to other parts of the body).⁹

Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts on their daily lives, particularly physical and emotional health, relationships and social life.¹⁰

CLINICAL NEED and BURDEN OF DISEASE

There are over 40,000 new cases of prostate cancer diagnosed every year in the UK.⁶ Prostate cancer is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65.¹¹ More than 50% of prostate cancer diagnoses in the UK each year are in men aged 70 years and over (2012 data), and the incidence rate is highest in men aged 90 years and over (2012–2014 data).

Out of every 10 prostate cancer cases, 4 (40%) are only diagnosed at a late stage in England (2014 data) and Northern Ireland (2010–2014 data). Incidence rates are projected to rise by 12% between 2014 and 2035 in the UK to 233 cases per 100,000 in 2035.¹²

In England in 2016, there were 40,489 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD-10 code C61).¹³ Considering that 40% of patients have late stage cancer at the time of diagnosis, the number of patients in 2016 out of 40,489 cases of prostate cancer with late stage prostate cancer would be around 16,196.

In UK in 2016, there were 11,631 deaths where malignant neoplasm of prostate (ICD-10 code C61) was recorded as the underlying cause. Incidence rates for prostate cancer are projected to rise by 12% in the UK between 2014 and 2035, to 233 cases per 100,000 males by 2035.¹⁴

Latest published survival statistics (2016, patients diagnosed in 2011-2015) report stated 1-year survival rate of 96.3% and 5-year survival rate of 88.3% (age-standardised) for patients with prostate cancer.¹⁵

According to the Hospital Episode Statistics (HES) data, in 2016-17 there were 70,295 admissions due to neoplasm of the prostate which resulted in 97,382 FCE bed days (ICD-10 code C61).¹⁶

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline in development. Prostate cancer: diagnosis and management (update) (GID-NG10057). Expected publication date: April 2019.
- NICE clinical guideline. Prostate cancer: diagnosis and management (CG175). January 2014.
- NICE interventional procedure guidance. Irreversible electroporation for treating prostate cancer (IPG572). December 2016.
- NICE interventional procedure guidance. Cryotherapy as a primary treatment for prostate cancer (IPG145). November 2005.

NHS ENGLAND and POLICY 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.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.

OTHER GUIDANCE

- Mottet N et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. 2017.¹⁷
- Comford et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. 2017.¹⁸
- NHS England. Guidelines for the Management of Prostate Cancer. 2016.¹⁹
- Parker C et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.²⁰

CURRENT TREATMENT OPTIONS

According to the NHS England, in patients with locally advanced disease the following treatment modalities can be considered:¹⁹

- At least 2 years of adjuvant androgen ablation (medical or surgical); oral anti-androgens may be considered (all patients)
- Hormonal treatment or watchful waiting (patients with short life expectancy, significant co-morbidities and minimal lower urinary tract symptoms (LUTS))

- Radical treatment including referral to a centre offering high dose-rate brachytherapy (other patients)

The following treatment options should be considered:¹⁹

- Hormone ablation (medical or surgical) (all patients)
- Surgical castration or LHRH antagonists (patients at very high risk of flare complications)
- Intermittent hormone therapy (patients with good response to Androgen Blockade Therapy (ABT))
- Docetaxel, abiraterone and enzalutamide (hormone resistant metastatic disease)

EFFICACY and SAFETY	
Trial	DKP 3M SC, NCT01715129 , 8-55-52014-200; triptorelin pamoate; phase III
Sponsor	Ipsen Ltd
Status	Completed
Source of Information	Trial registry ³
Location	Five EU countries [not UK]
Design	Single group assignment, open label
Participants	n=126 (enrolled); aged 18 years and older; prostate cancer; locally advanced and/or metastatic.
Schedule	11.25mg of triptorelin pamoate was given subcutaneously on day 1 and day 92 to patients
Follow-up	Not reported
Primary Outcomes	Percentage of subjects demonstrating castration at day 29 and maintaining castration at day 183 [time frame: at day 29 and 183]
Secondary Outcomes	<ul style="list-style-type: none"> • Percentage of subjects demonstrating castration before administration of the second dose [time frame: at day 92] • Probability of testosterone <50 ng/dL [time frame: day 29 through day 183] • Percentage of subjects demonstrating castration with testosterone level <50 ng/dL at Day 95 [time frame: day 95] • Time to achieve castration (Tcast) [time frame: up to day 36] • Plasma triptorelin levels (Cmin) [time frame: at day 92 and 183] • Percentage change in prostate specific antigen (PSA) levels from baseline in all subjects [time frame: from day 1 (baseline) to day 183 (end of study)] • Percentage of subjects with normal and abnormal PSA levels at day 183 (end of study visit) [time frame: at day 183] • Clinically apparent tumour progression [time frame: day 92 and 183] • Percentage of subjects with adverse events [time frame: up to day 183] • Time to Cmax (Tmax) of triptorelin [time frame: at 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours after first dose on day 1] • Peak plasma concentration value (Cmax) of triptorelin [time frame: at 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours after first dose on day 1] • Area under the concentration versus time curve between 0 and 24 Hours (AUC0-24) of triptorelin [time frame: at 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours after first dose on day 1] • Cmin of triptorelin in subset of 18 subjects [time frame: at day 92 and 183]

Key Results	Percentage of subjects demonstrating castration at day 29 and maintaining castration at day 183 was 97.6% (95% CI 93.2 to 99.5) and 96.6% (95% CI (91.6 to 99.1) respectively.
Adverse effects (AEs)	Serious adverse effects reported in the clinical trial included anaemia, cardiac failure, myocardial infarction, pneumonia, fibula fracture, chronic obstructive pulmonary disease
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Triptorelin is already marketed in the UK. The NHS indicative price for cisplatin vials is as follows:²¹

- Triptorelin (as triptorelin acetate) 3mg powder and solvent for injection (1 vial) costs £69.00 (Ipsen Ltd)
- Triptorelin (as triptorelin acetate) 3.75 mg powder and solvent for suspension for injection (1 pre-filled disposable injection) costs £81.69 (Ferring Pharmaceuticals Ltd)
- Triptorelin 11.25 mg powder and solvent for suspension for injection (1 vial) costs £207.00 (Ipsen Ltd)
- Triptorelin 11.25 mg powder and solvent for suspension for injection (1 vial) costs £248.00 (Ipsen Ltd)
- Triptorelin (as triptorelin embonate) 22.5 mg powder and solvent for suspension for injection (1 vial) costs £414.00 (Ipsen Ltd)

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other: | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input checked="" type="checkbox"/> Other: | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs Reduced drug treatment costs
- Other increase in costs: Other reduction in costs:
- Other: None identified

OTHER ISSUES

- Clinical uncertainty or other research question identified: None identified

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