

Luteinising hormone-releasing hormone (LHRH) agonists in prostate cancer

This bulletin focuses on luteinising hormone-releasing hormone (LHRH) agonists. Currently goserelin and leuprorelin (administered 4 weekly or 12 weekly and monthly or 3 monthly respectively) are the two LHRH agonists used primarily in the management of prostate cancer across England (88% share, ePACT October to December 2014). Triptorelin is also used for prostate cancer and has published data to confirm its efficacy. However triptorelin only accounts for 12% (ePACT October to December 2014) of all LHRH agonist usage.

Across England, a switch from 12 weekly goserelin and 3 monthly leuprorelin to 12 weekly or 6 monthly triptorelin **could result in an annual saving of £6.8 million** (ePACT October to December 2014).

Support materials (including the secondary care bulletin: Bulletin 28 Secondary care KPI support bulletins. Gonadorelin analogues – reduced usage of Zoladex) are available at <http://www.prescqipp.info>

Recommendations

- Engage and establish opinion with local Trust urologists on preferred formulary choices of LHRH agonists. This should take into account dosage intervals, administration, product price, and fees paid for administration. Local decision making may also be affected by local discounts and rebate scheme activity.
- 3 monthly and 6 monthly triptorelin and 3 monthly leuprorelin are the preferred cost effective LHRH agonists for prostate cancer in new patients.
- Switch guidance will need to be agreed by local Trust urologists for existing patients and should be considered at the next clinic appointment.
- Use 12 weekly/3 monthly or 6 monthly injections in preference to 4 weekly/monthly injections to support administration, convenience to the patient and costs.
- Review long term treatment in men with high risk localised prostate cancer. Androgen deprivation therapy may be considered for up to 3 years in this group. Intermittent therapy may be considered.¹

Background

Androgen deprivation treatment refers to treatments that act by reducing the effects of testosterone and other androgens, thus inhibiting the progression of prostate cancer. Any treatment ultimately resulting in the suppression of androgen activity is referred to as androgen deprivation or depletion therapy (ADT). Surgical castration was the first form of such treatment, but the main treatments now are the luteinising hormone-releasing hormone (LHRH; also called gonadotropin-releasing hormone [GnRH]) agonists and anti-androgens.²

Several hormonal therapies are licensed for use in prostate cancer. The LHRH agonists licensed for prostate cancer are:

- Goserelin (Zoladex® 3.6 mg implant and Zoladex® LA 10.8 mg)^{3,4}
- Leuprorelin (Prostap® 3 DCS and Prostap® SR DCS)^{5,6}
- Triptorelin (Decapeptyl® SR 3 mg, Decapeptyl® SR 11.25 mg, Decapeptyl® SR 22.5 mg)⁷⁻⁹

Licensed indications for leuprorelin and triptorelin have recently been updated and now all the LHRH agonists have indications of:³⁻⁹

- (i) Metastatic prostate cancer.
- (ii) Locally advanced prostate cancer, as an alternative to surgical castration.
- (iii) As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- (iv) As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.
- (v) As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

Another triptorelin product (Gonapeptyl ®depot 3.75 mg) is available, but it is licensed for the narrower indication of hormone-dependent locally advanced or metastatic prostate cancer.¹⁰ Other LHRH agonists licensed for use in prostate cancer, but not for these specific indications, are buserelin (Suprefact® nasal spray and Suprefact® injection) and histrelin (Vantas® 50 mg implant). Other hormonal therapies licensed for use in prostate cancer include the LHRH antagonist, degarelix and anti-androgens, such as cyproterone acetate, flutamide and bicalutamide.^{1,2}

National guidance

Guidelines from the European Association of Urology and the National Institute for Health and Care Excellence (NICE) on the diagnosis and treatment of prostate cancer recommend androgen deprivation treatment for metastatic prostate cancer.^{1, 11}

The NICE clinical guideline on the diagnosis and treatment of prostate cancer, which was updated in January 2014, recommends the following.

Men with low risk localised disease should be offered:

- Active surveillance or
- Radical treatment with prostatectomy (surgical removal of the prostate) or
- Radiotherapy.¹

Men with intermediate and high-risk localised prostate cancer should be offered a:

- Combination of radical radiotherapy and androgen deprivation therapy rather than radical radiotherapy or androgen deprivation therapy alone.
- Six months of androgen deprivation therapy before, during or after radical external beam radiotherapy.¹

Men with high risk localized prostate cancer:

- Consider continuing androgen deprivation therapy for up to 3 years and discussing the benefits and risks of this option with them.¹

Men with metastatic prostate cancer:

- Recommend androgen deprivation therapy as an option.¹

NICE also considers intermittent therapy for men having long-term androgen deprivation therapy (not in the adjuvant setting), and include discussion with the man, and his partner, family or carers if he wishes, about:

- The rationale for intermittent therapy and
- The limited evidence for reduction in side effects from intermittent therapy and
- The effect of intermittent therapy on progression of prostate cancer.¹

Clinical effectiveness

LHRH agonists such as goserelin, leuprorelin, and triptorelin induce castrate levels of testosterone by binding to their associated receptors in the anterior pituitary. This results in down regulation of the receptors, reducing luteinising hormone release from the pituitary and decreasing testosterone production by testicular Leydig cells. The initial stimulation of the receptors may lead to an initial flare-up of testosterone level, lasting up to 10 days. As a result of this flare, anti-androgens are given for the first two weeks. Castrate levels of testosterone (<1.74 nmol/L (< 50 ng/dL)) are reached within four weeks.²

There is limited comparative data of the different LHRH agonists.

- There is evidence that LHRH agonists are similar in effectiveness to surgical castration in terms of survival, testosterone suppression, symptom control and prostate volume reduction.^{1,11-13}
- A meta-analysis of 10 randomised controlled trials of 1908 patients with advanced prostate cancer found no significant difference in overall survival between LHRH agonists and surgical castration (hazard ratio 1.12, 95% confidence interval 0.915 to 1.386).¹²
- A NICE new medicine evidence summary for triptorelin SR states that the evidence on differences in adverse effects (e.g. impotence, hot flushes, glucose intolerance, increase risk of cardiovascular disease, osteoporosis) among the agents within each class is limited and does not suggest that one agent is superior to the others.¹⁴
- No dosage adjustment in elderly is required for the LHRH agonists.³⁻⁹

Taking cost effectiveness, route and frequency of administration into account, 6 monthly triptorelin and 3 monthly triptorelin and leuprorelin are the most cost effective products. However local Trusts and CCGs may wish to take any discounts and rebates into account which may affect the cost of the preparation.

Triptorelin

In 2013, the licensed indications for triptorelin (Decapeptyl® SR), were extended to include 2 new indications for prostate cancer:

- Neoadjuvant treatment before radiotherapy in high-risk localised or locally advanced disease, and
- Adjuvant treatment to radical prostatectomy in locally advanced disease at high risk of progression.⁷⁻⁹

The licensed indications for triptorelin were extended to be consistent with that of goserelin and leuprorelin. A NICE evidence summary states that these new indications are based on limited clinical data and extrapolation from evidence for other LHRH agonists.¹⁴ Of note is that whilst NICE guidelines support LHRH agonists as neoadjuvant treatment before radiotherapy, they do not recommend adjuvant hormonal therapy in addition to radical prostatectomy other than in the context of a clinical trial.¹

Triptorelin (Decapeptyl SR) is available in 3 formulations for prostate cancer:

- Decapeptyl SR 3 mg for intramuscular injection every 4 weeks (28 days),
- Decapeptyl SR 11.25 mg for intramuscular injection every 3 months, and
- Decapeptyl SR 22.5 mg for intramuscular injection every 6 months.

Patient factors

- Triptorelin (Decapeptyl SR) is supplied as a powder and solvent for suspension for injection and 2 needles (one for reconstitution and one for administration). It must be reconstituted using an aseptic technique and only using the ampoule of mannitol solution 0.8% for injection that is provided as the suspension vehicle with the 3 mg and 11.25 mg formulation or the ampoule of

‘water for injections’ that is provided with the 22.5 mg formulation.⁷⁻⁹

- Once the injection has been appropriately prepared in accordance with the manufacturer’s instructions the injection must be immediately administered to avoid precipitation.⁷⁻⁹
- Triptorelin is administered via a smaller sized needle (20 gauge) compared with goserelin LA 10.8mg (14 gauge) or goserelin 3.6mg (16 gauge) therefore minimising discomfort to patients.^{15,16} Triptorelin is given by intramuscular injection rather than a subcutaneous injection into the anterior abdominal wall and does not require use of a local anaesthetic.⁷
- Drugs which raise prolactin levels, e.g. antipsychotics should not be prescribed concomitantly as they reduce LHRH receptors in the pituitary. The SPCs advise caution with triptorelin and it is recommended that the patients’s hormonal status be supervised.⁷⁻⁹
- Subcutaneously administered LHRH agonists, goserelin or leuprorelin may be preferable in anticoagulated patients, rather than triptorelin which is administered intramuscularly.³⁻⁹

The NICE evidence summary concludes that local decision makers will need to consider the evidence for triptorelin alongside that for other LHRH agonists. Individual patient factors, and the licensed indications, dosage intervals and costs of the various LHRH agonists available will need to be taken into account in the context of NICE guidance.¹⁴

Leuprorelin

In May 2014, the licensed indications for leuprorelin (Prostap DCS), were extended to include a new indication for prostate cancer: Neoadjuvant treatment before radiotherapy in high-risk localised or locally advanced disease.^{5,6}

- Leuprorelin (Prostap DCS) is available in 2 formulations for prostate cancer:
 - » Prostap SR DCS (3.75mg) for intramuscular or subcutaneous injection every month.
 - » Prostap SR DCS (11.25mg) for subcutaneous injection every 3 months.
- Leuprorelin has been shown to significantly improve survival as both neo-adjuvant and adjuvant treatment to radiotherapy in patients with high-risk localised and locally advanced prostate cancer.^{17,18}
- Leuprorelin has not been compared with orchidectomy. However similar reductions in testosterone (to near castration levels in over 90% of patients) have been reported in uncontrolled trials and four trials comparing its effect with that of goserelin, triptorelin and diethylstilboestrol.^{5,19}

Patient factors

- Leuprorelin (Prostap DCS) is supplied as a powder and solvent for suspension in a pre-filled dual chamber syringe for injection, including a safety device. The pre-filled syringe of microsphere powder should be reconstituted immediately prior to administration by subcutaneous or intramuscular injection.^{5,6}
- Leuprorelin is administered via a smaller sized needle (23 gauge) compared with goserelin 10.8mg (14 gauge).²⁰
- Leuprorelin 3.75mg is given by intramuscular or subcutaneous injection while leuprorelin 11.25 mg is administered by a subcutaneous injection for prostate cancer and does not require use of a local anaesthetic.^{5,6}

Goserelin

- Goserelin (Zoladex implant) is available in two formulations for prostate cancer:
 - » Zoladex 3.6mg depot injected subcutaneously into the anterior abdominal wall every month.

- » Zoladex 10.8mg depot injected subcutaneously into the anterior abdominal wall every month.
- The evidence for goserelin is considered to be relatively strong for adjuvant use with radiotherapy, for localised and locally advanced prostate cancer. This was based on three randomised open-label trials of moderate quality showing clinically important positive effects on survival at five to ten years, compared with radiotherapy alone. There is also evidence for the use of goserelin plus flutamide as neoadjuvant to radiotherapy.²¹

Patient factors

The implant comes as an implant (a very small pellet) in a pre-filled syringe, ready to be used.

- The Midlands Therapeutic Review & Advisory Committee (MTRAC) commissioning support review states that when considering cost effectiveness and which product to use, patient frequency of GP surgery attendance, the frequency of drug administration and associated monitoring, and any GP practice fees for administration of the injections need to be taken into account. Fees for drug administration may vary as goserelin is an implant and leuprorelin is a liquid injection. MTRAC also states that commissioners should engage with providers to reach agreement on product use to achieve the most economic model for LHRH agonist use across the health economy. This should take into account product price and local discounts available from manufacturers.¹⁹

Table 1 on the next page provides a comparison of doses, frequency of administration and costs of LHRH agonists.

Table 1: Comparison of LHRH agonists³⁻⁹

Frequency	Monthly				3 monthly			6 monthly
Drug & dose	Goserelin 3.6mg	Leuprorelin 3.75mg	Triptorelin 3mg	Triptorelin 3.75mg	Goserelin 10.8mg	Leuprorelin 11.25mg	Triptorelin 11.25mg	Triptorelin 22.5mg
Brand name	Zoladex®	Prostap® SR DCS	Decapeptyl ® SR	Gonapeptyl® Depot	Zoladex® LA	Prostap® 3 DCS	Decapeptyl® SR	Decapeptyl ® SR
Form	Implant in prefilled syringe	Powder plus solvent in prefilled syringe	Powder for suspension with diluent	Powder for suspension with vehicle filled syringe	Implant in prefilled syringe	Powder plus solvent in prefilled syringe	Powder for suspension with diluent	Powder for suspension with diluent
Administration interval	28 days	Monthly	4 weekly	4 weekly	12 weekly	3 monthly	3 monthly	6 monthly
Needle safety device	Yes	Yes	No	No	Yes	Yes	No	No
Needle size	16 gauge	23 gauge	20 gauge	21 gauge ²²	14 gauge	23 gauge	20 gauge	20 gauge
Injection route	S/C	S/C or I/M	I/M	S/C or I/M	S/C	S/C	I/M	I/M
Cost per year ²³	£845	£902.88	£897	£1061.97	£1018.33	£902.88	£828	£828

Savings

Across England, over £82 million (ePACT October to December 2014) is spent annually on LHRH agonists.

88% of usage arises from goserelin and leuprorelin. 73% of all LHRH agonists are prescribed as 12 weekly/3 monthly preparations (ePACT October to December 2014).

Use 12 weekly/3 monthly injections (or 6 monthly triptorelin injections) in preference to 4 weekly/monthly injections to support administration, convenience to the patient and costs. If a switch is deemed suitable, consider a switch at the next clinic appointment from 12 weekly goserelin to 3 monthly or 6 monthly triptorelin or 3 monthly leuprorelin.

Switching goserelin (12 weekly) or leuprorelin (3 monthly) to triptorelin (3 monthly or 6 monthly) **could result in a potential annual saving of £6.8 million or £11,985 per 100,000 patients** (ePACT October to December 2014). Switch guidance will need to be agreed by local Trust urologists for existing patients and should be considered at the next clinic appointment.

If leuprorelin was preferred, as administration is via a prefilled syringe with a smaller sized needle, there would be an increased cost pressure if switching from triptorelin.

Switching goserelin (12 weekly) to leuprorelin (3 monthly) could result in a potential annual saving of £1.5 million or £2,658 per 100,000 patients (ePACT October to December 2014).

These switches should be considered through discussion with the patient at the next clinic appointment.

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Additional PrescQIPP resources



Briefing



Data pack

Available here: <http://www.prescqipp.info/resources/viewcategory/325-lhrh-analogues>

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