257 | April 2020 | 2.0

PrescQIPP Community Interest Company

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

In England and Wales, £76.5 million is spent annually on LHRH agonists. (NHSBSA Aug - Oct 2019).

Medicine optimisation projects in this area are aimed at switching goserelin (Zoladex® 3.6mg, Zoladex LA® 10.8mg) administered every 28 days or 12 weekly to three or six monthly triptorelin (Decapeptyl® SR 11.25mg or Decapeptyl® SR 22.5mg). If leuprorelin (Prostap®) is preferred to triptorelin (Decapeptyl®), then a switch from goserelin to three monthly leuprorelin (Prostap® 3 DCS) is recommended. Using three or six monthly triptorelin or three monthly leuprorelin in place of 28 days/monthly or 4 weekly goserelin, leuprorelin and triptorelin are also recommended as they are more convenient for patients and have reduced costs.

This bulletin reviews the place in therapy of LHRH agonists in prostate cancer and offers guidance and support materials for organisations considering reviewing LHRH agonists as a medicines optimisation project. LHRH agonist preparations are compared to support medicine formulary choice. The comparisons also support LHRH agonist selection for new patients.

Recommendations

- When deciding on LHRH agonist formulary choices in discussion with local Trust urologists, consider efficacy, safety, licensed uses, dosage intervals, administration, product price, and fees paid for administration.
- Local decision making may take account of local Trust discounts or primary care rebate scheme activity dependent upon local policies.
- Three monthly and six monthly triptorelin (Decapeptyl® SR 11.25mg and 22.5mg) and three monthly leuprorelin (Prostap® 3 DCS) are the preferred cost-effective LHRH agonists for prostate cancer in new patients.
- Use three monthly or six monthly LHRH agonist injections in preference to 28 days / four weekly / monthly injections as these are more convenient for patients and have reduced costs.
- Agree guidance on switches to cost-effective LHRH agonists with local Trust urologists for existing patients. Consider switches suitable for the individual patient at the next clinic appointment.
- Review long-term LHRH agonist treatment in men with high risklocalised prostate cancer. Consider using intermittent androgendeprivation therapy (ADT) with monitoring in men with high risklocalised prostate cancer who are on long term (up to three years) ADT.[1]
- Engage with and establish opinion from local Trust urologists on the use of intermittent LHRH agonist therapy. Where intermittent therapy is appropriate the urologist should discuss this with patients (including risks and benefits as recommended by NICE). The urologist should inform the GP if the patient is to be treated with LHRH agonist intermittent therapy and provide details of the monitoring requirements.

Background

Prostate cancer is the most common cancer in men and the second most common cancer in the UK. Over 50% of cases in the UK are diagnosed in men age 70 years and over. There were approximately 11,000 deaths from prostate cancer in 2014 in the UK. Incidence rates are projected to rise by 12% between 2014 and 2035 in the UK.[2]

ADT refers to treatments that act by reducing the effects of testosterone and other androgens, thus inhibiting the progression of prostate cancer.[3] Any treatment ultimately resulting in the suppression of androgen activity is referred to as androgen deprivation or depletion therapy. Surgical castration was the first form of such treatment, but the main treatments now are the LHRH agonists/antagonists and anti-androgens.[3,4] Luteinising hormone-releasing hormone is also referred to as gonadotropin-releasing hormone (GnRH).[3] LHRH agonists (leuprorelin, goserelin and triptorelin) are first-line treatments for hormone-dependent prostate cancer. Clinicians consider each LHRH agonist to have equivalent clinical efficacy.[4]

Most men who receive ADT for prostate cancer will receive the treatment for anything between a few months up to a few years.[1] The Prostate Cancer Charity estimate that around 9,000 newly diagnosed men in the UK will receive ADT each year; around 26% of all new diagnoses.[2] The Prostate Cancer Charity found 43% of respondents had received ADT for localised disease, 33% for locally advanced, and 22% for advanced disease. Of all respondents, 73% were currently receiving ADT.[2] GPs (53%) and practice nurses (40%) were most commonly cited as the healthcare professional involved in the provision of ADT.

The LHRH agonists licensed for prostate cancer are:

- Goserelin (Zoladex® 3.6 mg implant; Zoladex LA® 10.8 mg)[5,6]
- Leuprorelin (Prostap® 3 DCS; Prostap® SR DCS; Lutrate® *)[7,8,9]
- Triptorelin (Decapeptyl® SR 3 mg; Decapeptyl® SR 11.25 mg; Decapeptyl® SR 22.5 mg; Gonapeptyl® Depot)[10-13]

*Manufacturing of Lutrate® discontinued in December 2018.[9]

All LHRH agonists, except Gonapeptyl® Depot, are licensed for the following indications:[5-8,10-13]

- Metastatic prostate cancer.
- Locally advanced, non-metastatic 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.

Gonapeptyl® Depot 3.75mg is only licensed for the narrower indication of hormone-dependent locally advanced or metastatic prostate cancer.[13]

Buserelin, an LHRH agonist, is licensed for use in prostate cancer, but not for these specific indications. Other hormonal therapies licensed for use in prostate cancer include the LHRH antagonist, degarelix and anti-androgens, such as cyproterone acetate, flutamide and bicalutamide.[14] These preparations are not considered in this bulletin.

National guidance

The NICE guideline (NG131) on the diagnosis and management of prostate cancer makes the following recommendation on when to offer or consider ADT:[1,2]

- Offer people with intermediate- and high-risk localised prostate cancer (also referred to as locally advanced prostate cancer) a combination of radical radiotherapy and ADT, rather than radical radiotherapy or ADT alone.
- Offer people with intermediate- and high-risk localised prostate cancer six months of ADT before, during or after radical external beam radiotherapy. The optimal timing and overall duration of ADT is uncertain.
- Consider continuing ADT for up to three years for people with high-risk localised prostate cancer, and discuss the benefits and risks of this option with them.
- Consider intermittent therapy for people having long-term ADT (not in the adjuvant setting). Discuss with the person (and their partner, family or carers if they wish):
  - the rationale for intermittent therapy
  - the limited evidence for reduction in side effects from intermittent therapy
  - the effect of intermittent therapy on progression of prostate cancer.
- For people who are having intermittent ADT: measure PSA every three months and restart androgen deprivation therapy if PSA is 10ng/ml or above, or if there is symptomatic progression.
- Begin ADT and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.
- Offer bilateral orchidectomy as an alternative to continuous LHRH agonist therapy.
- NICE do not recommend offering hormonal therapy:[1,2]
  - In addition to radical prostatectomy for locally advanced prostate cancer, even to men with margin-positive disease, other than in the context of a clinical trial.
  - In biochemical relapse post radical prostatectomy or radiotherapy unless men have symptomatic local disease progression or any proven metastases or a PSA doubling time of less than 3 months.
- NICE recommends ADT for metastatic prostate cancer.[1,2]

The European Association of Urology advises that LHRH agonists are currently the main forms of ADT.[15]

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 ten days. As a result of this flare, anti-androgens are given for the first two weeks.[3] Patients should be reviewed to ensure that anti-androgen therapy is stopped when appropriate. Castrate levels of testosterone (<1.74nmol/L (<50ng/dL)) are reached within four weeks.[3]

Although there is no formal direct comparison between the LHRH agonists, they are considered to be equally effective and comparable to orchidectomy.[15]

From the limited comparative data for the different LHRH agonists:

- There is evidence that LHRH agonists are similar in effectiveness to surgical castration in terms of survival and testosterone suppression.[15,16]

- A meta-analysis of ten randomised controlled trials of 1,908 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).[16]
- The evidence on differences in adverse effects (e.g. impotence, hot flushes, glucose intolerance, increased 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.[14,16]
- No dosage adjustment in elderly is required for any of the LHRH agonists.[5-8,10-13]

The LHRH agonist preparations have practical differences, including:[15]

- Storage temperature.
- Require reconstitution before use or are ready for immediate use.
- Given by subcutaneous or intramuscular injection.

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

Triptorelin

Triptorelin is available in four formulations for the management of prostate cancer:[10-13]

- Decapeptyl® SR 3mg for intramuscular injection every four weeks (28 days).
- Decapeptyl® SR 11.25mg for intramuscular injection every three months.
- Decapeptyl® SR 22.5mg for intramuscular injection every six months (24 weeks).
- Gonapeptyl® Depot 3.75mg powder and solvent for suspension for injection prolonged release in pre-filled syringes every four weeks (28 days).

Decapeptyl® SR is licensed for:[10-12]

- Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration.
- Treatment of metastatic prostate cancer.
- As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- As a neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

The last two indications were approved in 2013 and makes the licensed indications for Decapeptyl® SR the same as for 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]

Gonapeptyl® Depot 3.75mg is only licensed for the treatment of hormone dependent locally advanced or metastatic prostate cancer.[13]

Patient factors

- Decapeptyl® SR is supplied as a powder and solvent for suspension for injection and 2 needles (one for reconstitution without a safety device and one for intramuscular administration, 20 gauge with a safety device). 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 3mg and 11.25mg formulation or the ampoule of 'water for injections' that is provided with the 22.5mg formulation.[10-12] Once the injection has been made it must be immediately administered to avoid precipitation from the resulting suspension.[10-12]
- Gonapeptyl® Depot 3.75mg is supplied as a powder and solvent for making a suspension for injection prolonged release in pre-filled syringes, these are connected immediately prior to use. The suspension should be administered either subcutaneously (SC) or by deep intramuscular injection (IM) within three minutes of reconstitution.[13] The pack is provided with a 21-gauge green (IM) needle and a 27-gauge grey (SC) needle.[17]
- Decapeptyl® SR formulations and Gonapeptyl® Depot 3.75mg are administered using a smaller sized needle (20 or 21 gauge) compared to Zoladex® (goserelin) formulations - long acting (LA) 10.8mg (14 gauge) or 3.6mg (16 gauge). Smaller needle size should minimise discomfort to patients.[5,6,10-12,18,19]
- Decapeptyl® SR is administered by intramuscular injection, compared to Zoladex® which is administered by a subcutaneous injection into the anterior abdominal wall.[5,6,10-12]
- Drugs which raise prolactin levels should not be prescribed concomitantly with triptorelin as they reduce LHRH receptors in the pituitary. The patient's hormonal status be supervised if triptorelin is co-administered with drugs affecting pituitary secretion of gonadotropins.[10-12]
- Intramuscular injections should be avoided where possible in patients taking an oral anticoagulant.[20] Subcutaneously administered LHRH agonists preparations may be preferable in anticoagulated patients, e.g. Zoladex®, Prostap®, Gonapeptyl® Depot, rather than Decapeptyl® SR which is administered intramuscularly.[5-8, 10-13]
- 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

- Leuprorelin is available in two formulations for prostate cancer:[7,8]
  - » Prostap® SR DCS 3.75mg for intramuscular or subcutaneous injection every month.
  - » Prostap® 3 DCS 11.25mg for subcutaneous injection every three 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.[7,8]
- 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.[21] In a meta-analysis involving primarily patients with metastatic disease, no statistically significant difference in survival was found for patients treated with LHRH analogues compared with patients treated with orchidectomy.[7,8]

Patient factors

- Prostap® SR DCS and Prostap® 3DCS are 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.[7,8]
- Prostap® SR DCS and Prostap® 3 DCS injections are administered using a smaller sized needle (23 gauge).[7,8]
- Prostap® SR DCS 3.75mg is given by intramuscular or subcutaneous injection while Prostap® 3 DCS 11.25mg is administered by a subcutaneous injection for prostate cancer.[7,8]

Goserelin

- Goserelin (Zoladex® implant) is available in two formulations for prostate cancer:
  - Zoladex® 3.6mg depot injected subcutaneously into the anterior abdominal wall every 28 days.[5]
  - Zoladex LA® 10.8mg depot injected subcutaneously into the anterior abdominal wall every 12 weeks.[6]
- 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.[22]

Patient factors

Zoladex® depot injections are supplied as an implant (a very small pellet) in a pre-filled syringe, ready to be used.[5,6]

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 considered.[21] 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.[21]

Table 1 provides a comparison of doses, frequency of administration and costs of LHRH agonists.

Table 1: Comparison of LHRH agonists[5-8,10-13,17-19,23]

= Preferred choices

Frequency	Monthly (28 days)				3 monthly			6 monthly
Drug & dose	Triptorelin 3mg	Leuprorelin 3.75mg	Goserelin 3.6mg	Triptorelin 3.75mg	Triptorelin 11.25mg	Leuprorelin 11.25mg	Goserelin 10.8mg	Triptorelin 22.5mg
Brand name	Decapeptyl® SR 3mg	Prostap® SR DCS 3.75mg	Zoladex® 3.6mg	Gonapeptyl® Depot 3.75mg	Decapeptyl® SR 11.25mg	Prostap® 3 DCS 11.25mg	Zoladex LA® 10.8mg	Decapeptyl® SR 22.5mg
Form	Powder for suspension with diluent	Powder plus solvent in prefilled syringe	Implant in prefilled syringe	Powder for suspension with vehicle filled syringe	Powder for suspension with diluent	Powder plus solvent in prefilled syringe	Implant in prefilled syringe	Powder for suspension with diluent
Refrigeration required?	No	No	No	Yes	No	No	No	No
Preparation	Requires reconstitution	Requires reconstitution	Ready to use	Requires reconstitution	Requires reconstitution	Requires reconstitution	Ready to use	Requires reconstitution
Administration interval	4 weekly	28 days	28 days	4 weekly	3 monthly	3 monthly	12 weekly	6 monthly
Needle safety device	No	Yes	Yes	No	No	Yes	Yes	No
Needle size	20 gauge	23 gauge	16 gauge	21 gauge	20 gauge	23 gauge	14 gauge	20 gauge
Injection route	IM	S/C or I/M	S/C	S/C or I/M	I/M	S/C	S/C	I/M
Cost per year	£897	£902.88	£910	£1061.97	£828	£902.88	£1018.33	£828

Savings

Across England and Wales, £76.5 million (NHSBSA Aug – Oct 2019) is spent annually on LHRH agonists.

Switches to three or six monthly triptorelin or three monthly leuprorelin reduce the number of injections per year which would be more convenient for patients.

Switching goserelin (Zoladex® 3.6mg, Zoladex LA® 10.8mg), leuprorelin (Prostap® SR 3mg, Prostap® 3 DCS, Decapeptyl® SR 3mg, Gonapeptyl® Depot) to three or six monthly triptorelin (Decapeptyl® SR 11.25mg or Decapeptyl® SR 22.5mg) would reduce the number of injections administered per year and **result in a potential saving of £9.8 million per year across England and Wales. This equates to £15,531 per 100,000 population.**

If leuprorelin (Prostap®) is preferred to triptorelin (Decapeptyl®), then a switch from goserelin (Zoladex® 3.6mg, Zoladex LA® 10.8mg) to three monthly leuprorelin (Prostap® 3 DCS) is recommended. **This could result in potential savings of £3.7 million per year across England and Wales. This equates to £5,972 per 100,000 population.**

Any switches to cost-effective alternatives should be considered through discussion with the patient at the next clinic appointment.

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Additional PrescQIPP resources

	Bulletin	https://www.prescqipp.info/our-resources/bulletins/bulletin-257-lhrh-agonists-in-prostate-cancer/
	Implementation tools	
	Data Pack	https://pdata.uk/#/views/B257_LHRHanalogues/FrontPage?:iid=1

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