Arden and Greater East Midlands Commissioning Support Unit in association with Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services, United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

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REVIEW OF GONADOTROPIN RELEASING HORMONE AGONISTS FOR PROSTATE CANCER

- **Gonadotropin releasing hormone (GnRH) agonists such as goserelin, leuprorelin and triptorelin given as long acting sub-cutaneous or intra-muscular injections have a well-established, NICE endorsed role as hormonal therapy in the treatment of prostate cancer.**
- **There is no conclusive evidence to suggest that one GnRH agonist is more effective than another in the treatment of prostate cancer. NICE do not recommend a preferred agent, but suggest that selection should be based on licensed indications, tolerability, administration schedule and cost effectiveness.**
- **Triptorelin intramuscular injection (*Decapeptyl*) has the full range of marketing authorisations for prostate cancer, has a finer needle than goserelin (*Zoladex*), is lower cost than *Zoladex* and leuprorelin (*Prostap*) and has a six monthly IM preparation for increased patient convenience. Prescribers are urged to review all of their patients currently receiving a gonadotropin releasing hormone agonist for prostate cancer to ensure that, wherever possible, treatment is standardised around first line triptorelin (*Decapeptyl*). Where a second line option is required, leuprorelin (*Prostap*) is preferred. Both products are designated AMBER without shared care and are approved for first and second line use respectively where a GnRH agonist is indicated for prostate cancer.**
- **Goserelin (*Zoladex*) is the only GnRH agonist licensed for the treatment of breast cancer and is included on the *Lincolnshire Joint Formulary* solely for this indication; designation: AMBER without shared care.**
- **All three of the GnRH agonists have attractive purchasing deals. Further information is available from the respective manufacturers.**
- **Following review within United Lincolnshire Hospitals, urologists and other specialists initiating GnRH agonist therapy have agreed to specify triptorelin or leuprorelin as the preferred first line GnRH agonists of choice. Goserelin (*Zoladex*) will only be specified by name within the context of breast cancer treatment. A copy of the revised ULH Out-Patient Letter specifying the two preferred options is included as an Appendix to this *Bulletin*.**
- **The potential annual savings across all four Lincolnshire CCGs assuming 100% switch to triptorelin is £196,693. Most of this saving could be realised by focussing solely on review and switch of patients currently prescribed goserelin 10.8mg (*Zoladex LA*).**

Background

NICE Clinical Guideline 175, *Prostate cancer diagnosis and treatment* (2014)

- NICE recommend that men with localised prostate cancer should be offered active surveillance or radical treatment with prostatectomy (surgical removal of the prostate) or radiotherapy.
- For men with intermediate and high risk localised prostate cancer, a combination of radical radiotherapy and androgen deprivation therapy (also known as hormonal therapy), rather than radical radiotherapy or androgen deprivation therapy alone is recommended. Androgen deprivation therapy is recommended for 6 months before, during or after radical external beam RT.
- Consideration should be given to continuing androgen deprivation therapy for up to 3 years in men with high-risk localised prostate cancer subject to an evaluation of risks and benefits.
- Androgen deprivation therapy is also recommended for men with prostate cancer who experience a biochemical relapse after radical (prostatectomy or RT) treatment if they have symptomatic local disease progression, metastases or a prostate specific antigen (PSA) doubling time of less than 3 months.
- There is no conclusive evidence to suggest that one GnRH agonist is more effective than another in the treatment of prostate cancer. NICE do not recommend a preferred agent, but suggest that selection should be based on licensed indications, tolerability, administration schedule and cost effectiveness.

Licensed indications (Updated June 2016)

- The gonadorelin releasing hormone agonists licensed for use in prostate cancer are: goserelin, leuprorelin, triptorelin, buserelin and histrelin. The licensed indications of the key products are tabulated below. Other hormonal therapies licensed for use in prostate cancer include degarelix (a LHRH antagonist) and anti-androgens such as cyproterone acetate, flutamide and bicalutamide.

Drug and 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 # needle size can be a problem**	**Powder plus solvent in prefilled syringe**	**Powder for suspension with diluent**	**Powder for suspension with vehicle in pre-filled syringe**	**Implant in prefilled syringe # needle size can be a problem**	**Powder plus solvent in prefilled syringe**	**Powder for suspension with diluent**	**Powder for suspension with diluent**
Injection frequency	**28 days**	**Monthly**	**4 weekly**	**28 days**	**12 weekly**	**3 monthly**	**3 monthly**	**6 monthly**
Licensed uses								
CaP metastatic	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CaP locally advanced alternative to castration	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CaP adjuvant treatment to radiotherapy	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**
CaP neo adjuvant prior to radiotherapy	**Yes**	**No**	**Yes**	**Noi**	**Yes**	**No**	**Yes**	**Yes**
CaP adjuvant	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**

treatment to radical prostatectomy								
Endometriosis	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**No**
Uterine fibroids	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**No**
Advanced breast cancer	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Early breast cancer	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Precocious puberty	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**Yes**	**No**
Endometrial thinning	**Yes**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**
Assisted reproduction	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Endometrial preparation prior to intrauterine surgical procedures	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**

PACEF Recommendation:
All three of the key GnRH agonists are licensed for the full range of prostate cancer indications. Goserelin (*Zoladex*) is the only product licensed for the treatment of breast cancer and is included on the *Lincolnshire Joint Formulary* for this indication; designation AMBER without shared care.

Tolerability

- Goserelin 3.6mg and 10.8mg (*Zoladex* and *Zoladex LA*) are both administered as a sub-cutaneous implant through a prefilled syringe. The size of the needle involved can prove off-putting and painful for some patients; alternative preparations, such as leuprorelin (*Prostap*) and triptorelin (*Decapeptyl*), which have a smaller needle and are less painful, may be preferred.

Administration schedule

- Injection frequency is an issue for both clinicians and patients. All three products are available in three monthly injections within licensed indications (i.e. goserelin 10.8mg (*Zoladex LA*), leuprorelin 11.25mg (*Prostap 3 DCS*) and triptorelin 11.25mg (*Decapeptyl SR*)). Triptorelin is also available as a 22.5mg 6 monthly injection (*Decapeptyl SR*).

PACEF Recommendation:
Prescribers are urged to review existing patients on *Zoladex* or *Zoladex LA* with a view to moving patients with prostate cancer to a more comfortable and longer-acting product such as 3 or 6 monthly triptorelin (*Decapeptyl SR)* or 3 monthly leuprorelin 11.25mg (*Prostap 3 DCS*). Ipsen, the manufacturer of the *Decapeptyl* range of products, can provide useful materials to support such a switch, including patient leaflets.

Cost Comparison

Product	Cost per dose NHS List Price September 2016	Cost for 12 months treatment
Triptorelin 11.25mg (*Decapeptyl SR*) 3 monthly (Ipsen Ltd)	£207	£828
Triptorelin 22.5mg (*Decapeptyl SR*) 6 monthly (Ipsen Ltd)	£414	£828
Goserelin 10.8mg (*Zoladex LA*) 3 monthly (AstraZeneca UK Ltd)	£235	£940
Leuprorelin 11.25mg (*Prostap 3 DCS*) 3 monthly (Takeda UK Ltd)	£225.72	£902.88

PACEF Recommendation

A cost comparison of 3 and 6 monthly products reveals that triptorelin IM injection 11.25mg and 22.5mg (*Decapeptyl SR*) is currently the most cost-effective GnRH agonist for prostate cancer. The highest cost product by a significant margin is goserelin 10.8mg (*Zoladex LA*).

Purchasing arrangements

All three of the GnRH agonists have attractive purchasing deals. Further information is available from the respective manufacturers.

Potential cost savings

The table below details the estimated cost saving per year for each of the Lincolnshire CCGs assuming either a 100% switch or a 50% switch from goserelin and leuprorelin to equivalent dose triptorelin. Goserelin 3.6mg is excluded from the switch as some, if not all, of its use could be for breast cancer. Figures are based on 2015/16 data.

Switch	LECCG	LWCCG	SLCCG	SWLCCG
Goserelin depot 10.8mg to Triptorelin 11.5mg	£33,732	£44,059	£29,015	£20,418
Leuprorelin 3.75mg to triptrorelin 3mg	£358	£191	£160	£152
Leuprorelin 11.25mg to triptorelin 11.25mg	£25,728	£12,543	£21,328	£9,009
Potential annual savings (100%)	£59,818	£56,793	£50,503	£29,579
Potential annual savings (50%)	£29,909	£28,396	£25,251	£14,789

The potential annual savings across all four CCGs is £196,693 (assuming 100% switch). Most of this saving could be realised by focussing solely on goserelin 10.8mg (*Zoladex LA*).

Ipsen, the manufacturer of triptorelin (Decapeptyl), have produced resources including patient information leaflets and other materials to support switches to triptorelin from alternative therapies.

Summary

Triptorelin intramuscular injection (*Decapeptyl*) has the full range of marketing authorisations for prostate cancer, has a finer needle than goserelin (*Zoladex*), is lower cost than *Zoladex* and leuprorelin (*Prostap*) and has a six monthly IM preparation for increased patient convenience. Prescribers are urged to review all of their patients currently receiving a GnRH agonist for prostate cancer to ensure that, wherever possible, treatment is standardised around first line triptorelin (*Decapeptyl*). Where a second line option is required, leuprorelin (*Prostap*) is preferred. Both products are designated AMBER without shared care and are approved for first and second line use respectively where a GnRH agonist is indicated for prostate cancer. ULH urologists and oncologists have produced a standard letter for issue from their out-patient clinics requesting that GPs initiate either triptorelin (Decapeptyl) three or six monthly or leuprorelin (Prostap) in new patients (see Appendix).

Acknowledgements

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References:

NICE Clinical Guideline 175, *Prostate cancer: diagnosis and treatment* (January 2014).

NICE Evidence summary: new medicine*, Prostate cancer: triptorelin (Decapeptyl SR)* (January 2014)

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December 2016

United Lincolnshire Hospitals NHS
NHS Trust

Outpatient Services

Report Summary to General Practitioner from Doctor/Non-Medical Prescriber attending the patient in clinic

Patient ID Label

Dear Doctor

Your patient was seen by me on ……when attending for a clinic appointment

A full report will follow as soon as possible

a) I would be grateful if you would consider making the following changes to their medication, at their next prescription renewal date. The changes have been discussed with the patient, including a brief explanation of any potential side effects associated with new medication.

Please add new medication: Bicalutamide tablet 50 mg daily (for 21 days) and then

☐ DECAPEPTYL 11.25 mg injection three monthly

☐ DECAPEPTYL 22.5 mg injection six monthly

☐ LEUPRORELIN 11.25 mg injection every 12 weeks

First injection should be 3 – 5 days after having started Bicalutamide

(Tick preferred choice)

Clinical indication Hormone treatment for prostate cancer

Please stop the following medication ……
Reason for stopping ……
Please change dosage of following medication ……..
Reason for change ……

b) I have issued a prescription for ……

for ……days, It is to be continued for ……..

c) I will review again on ……..and keep you updated on their progress.

Thank you for your help.

Yours sincerely
Name of Prescriber (PRINT): …… Consultant.

United Lincolnshire Hospitals NHS
NHS Trust

To the PATIENT:

Your specialist/consultant in the hospital has recommended to your GP that there should be a change to your current treatment. This may require a new drug to be started, on old drug to be stopped or the dose of an existing drug changed.

These changes are **NOT** considered urgent.

Please leave this form at your doctor's surgery as soon as possible after your out-patient appointment so that your GP is made aware of the changes required and can organise a revised prescription for you.

Please allow **SEVEN** days from your out-patient appointment before returning to the surgery to collect your prescription. This will allow your surgery adequate time to process the form and to issue a revised prescription.

Remember, your specialist has decided that these changes to your treatment are **NOT URGENT**. Do not book an appointment with your GP to discuss this further or to organise a prescription, unless you have specific concerns or are requested to do so by your surgery.

Thank you

Issued by OUT-PATIENTS DEPARTMENT
UNITED LINCOLNSHIRE HOSPITALS NHS TRUST