789FM.1 GONADORELIN ANALOGUES (GnRHa): TRIPTORELIN, GOSERELIN, LEUPRORELIN FOR PROSTATE CANCER - AMBER RECOMMENDATION GUIDELINE

This guideline provides prescribing and monitoring guidance for triptorelin, goserelin and Leuprorelin use in prostate cancer. It should be read in conjunction with the Summary of Product Characteristics (SPC), available on www.medicines.org.uk/emc, and the BNF.

BACKGROUND AND INDICATIONS FOR USE

There is no conclusive evidence to suggest that any one GnRHa is more effective or has fewer side effects than another for the treatment of prostate cancer.[5, 7-9] Available evidence suggests that GnRHa are similar in effectiveness to surgical castration. They have the same licensed indications in the treatment of prostate cancer (Appendix 1). Appendix 2 compares doses, administration frequency and costs.[1-4, 9-13]

Triptorelin 22.5 mg (six monthly injection) is the 1st choice GnRHa for treatment of metastatic prostate cancer patients on life-long treatment on the Bucks formulary. This is because it is:

- Administered via a smaller sized needle (20 gauge) compared to goserelin LA 10.8 mg (14 gauge), thus minimising discomfort to patients.[9]
- The least expensive in terms of drug and administration costs (Appendix 2).[1-4, 9-13]

Triptorelin 22.5 mg (six monthly injection) is not preferred in:

- Patients newly initiated GnRHa because the first dose should be a monthly preparation (Decapeptyl® SR 3 mg) in order to check that the product is tolerated prior to changing to the six monthly preparation.[14]
- Anticoagulated patients. This is because triptorelin is an intramuscular (IM) injection. Subcutaneously administered GnRHa (goserelin or leuprorelin) may be preferable.[9]

RESPONSIBILITIES

Hospital specialist

1. Diagnosis of the condition. Ensure that other treatment options have been fully explored.
2. Pre-treatment tests.
3. Recommend initiation of the most cost-effective GnRHa and bicalutamide (where appropriate).
4. Document the diagnosis and treatment details (timing, dose, duration and administration).
5. Outline to the GP when therapy may be reduced and stopped, assuming no relapse.
6. Agree review periods for each patient (see Monitoring and Specialist review period below).
7. Respond to issues raised by the GP after the patient has been transferred.
8. Advise the GP on related issues, e.g. drug interactions, management of related problems.

GP

9. Monitor patients' overall health and wellbeing and raise any concerns regarding any complication of treatment with the specialist, if appropriate.
10. Prescribe GnRHa (usually triptorelin). Prescribe the monthly preparation (triptorelin 3 mg) for the first month. This is followed by the 6 monthly preparations (triptorelin 22.5 mg).
11. If recommended by the specialist, prescribe bicalutamide (see dosing below). If initiation of the GnRHa is urgent, the specialist may initiate bicalutamide and advise the GP of the date to start the first dose of GnRHa.
12. Administer GnRHa (in conjunction with practice nurses where appropriate).
13. Monitor response and adverse drug reactions (ADRs).
14. Monitor prostate specific antigen (PSA) 3 months after starting the GnRHa and then every 6 months (see Monitoring below).
15. Seek advice from the specialist if there is significant change in the patient's condition.
16. Reduce or stop treatment in line with the specialist's original request.

Guidance on switching patients to Triptorelin 22.5 mg six monthly injection
(ONLY for metastatic prostate cancer patients requiring lifelong GnRHa)

- Uro-oncologists at Buckinghamshire Healthcare NHS Trust (BHT) recommend switching **existing metastatic prostate cancer** patients already on **life-long** monthly or 3 monthly goserelin, leuprorelin, or triptorelin injections to triptorelin 22.5 mg six monthly injections.
- The switch is not required for any other prostate cancer indications unless recommended by the specialist.
- The switch to the triptorelin six monthly preparations does not require prior administration of the triptorelin monthly preparation.
- The switch should not cause any potential testosterone flare. Clinical experience shows that when a GnRHa is intentionally stopped (particularly in patients on long term treatment), an extended period of time usually ensues before a rise in testosterone levels is noted.[9]
- GPs can switch patients to triptorelin 22.5 mg 6 monthly injection at the patient's next GnRHa administration appointment.
- GPs should inform patients of the change in treatment.

SUPPORTING INFORMATION

CONTRAINDICATIONS AND PRECAUTIONS [1-4, 10-13]

1. No dose adjustment is required in the elderly or in renal or liver impairment.
2. If using blood glucose monitoring strips (e.g. in type 1 diabetes) patients may require more frequent monitoring of blood glucose levels. If not using strips, an HbA_{1c} check (e.g. most type 2 diabetics) is recommended with the PSA for the first year.
3. Prolonged use may lead to bone loss, enhancing the risk of osteoporosis. Consider assessing fracture risk in particular if other risk factors are present i.e. previous fragility fracture, steroid treatment etc. **Prevention of tumour 'flare' reactions.**
    - During the initial stage of GnRHa treatment, increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour 'flare' may cause spinal cord compression, ureteric obstruction or increased pain[16]. It should be closely supervised in the first month of treatment.
    - Concomitant use of bicalutamide 50 mg PO once daily may be recommended by the specialist for some patients. Bicalutamide is started 7 to 10 days prior to initiating the GnRHa and is continued for 28 days. The bicalutamide treatment duration will be specified by the specialist at the time of recommending initiation of the GnRHa. If the GnRHs needs to be started urgently, the specialist may prescribe it and then inform the GP of the date when the first GnRHa dose needs to be administered.

DOSES AND ADMINSTRATION - See Appendix 2 below.

TIME TO RESPONSE

PSA will drop within 3 months if the patient is responding to treatment. The PSA should therefore be checked 3 months after treatment initiation.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

Clinical assessment and examination.
Urea and electrolytes (U&E), full blood count (FBC), PSA investigations performed at outpatient appointment.

MONITORING SCHEDULES

PSA: 3 months after the first dose of GnRHa and then every 6 months.

Specialist review period:

- Every 3 months if the patient or PSA is unstable (if the GP has concerns, the patient may be referred back earlier).
- Every 6 - 12 months if the patient remains well and the PSA is stable.

Common adverse effects	Uncommon adverse effects
Worsening of existing symptoms during tumour flare	Mood change
Hot flushes	Breast swelling or tenderness
Decreased libido and impotence	Headache (occasionally severe), migraine
Bone and joint pain (may be increased initially)	Changes in blood lipids
Injection site reactions (pain, mild bruising and erythema)	Hypotension or hypertension
Sweating	Nausea, gastrointestinal (GI) disturbance
Weight gain	

Hypersensitivity reactions, including rash, urticaria, pruritis, and rarely, wheezing, interstitial pneumonitis or worsening of asthma have been reported. Anaphylactic reactions are rare.
For rare ADRs see SPC.[1]

DRUG INTERACTIONS - see SPC for full list at http://www.medicines.org.uk/emc/

Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of GnRH receptors in the pituitary (e.g. antipsychotics such as risperidone, olanzapine, quetiapine, and haloperidol).

BACK-UP INFORMATION/ADVICE

For advice contact the specialist who saw your patient:

Urology	Tel	Email
Mr J Greenland	01296 315189	jonathan.greenland@nhs.net
Mr A Bdesha Mr N Haldar	01494 426005	amar.bdesha@nhs.net n.haldar@nhs.net bht.urologysecretaries@nhs.net
Oncology		
Dr P Chakraborti	01494 426314 (sec)	p.chakraborti@nhs.net
Medicines Resource Centre	01494 425355	
BHT switchboard	01296 315000	

Acknowledgement
Some sections of this guideline have been adapted from the Oxfordshire CCG guideline GnRH analogues in prostate cancer updated 2017 https://www.oxfordshireccg.nhs.uk/professional-resources/documents/clinical-guidelines/cancer/gonadotropin-releasing-hormone-GnRH-analogues-in-prostate-cancer.pdf.

REFERENCES

1. Summary of Product Characteristics. Decapeptyl® SR 22.5 mg. Ipsen Ltd. Last updated 06/05/2016. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/5906/smpc
2. Summary of Product Characteristics. Decapeptyl® SR 11.25 mg. Ipsen Ltd. Last updated 05/07/2017. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/780/smpc
3. Summary of Product Characteristics. Decapeptyl® SR 3 mg Ipsen Ltd. Last updated 08/09/2017. Accessed on 19/18/2020 via https://www.medicines.org.uk/emc/product/963/smpc
4. Summary of Product Characteristics. Gonapeptyl Depot® 3.75 mg. Ferring Pharmaceuticals Ltd. Last updated May 2015. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/2229
5. London New Drugs Group APC/DTC Briefing Document. Triptorelin and GnRH Analogues Review. Feb 2007 (updated Nov 2007).
6. Drug tariff. NHSBSA prescription services. January 2020. Available via https://www.nhsbsa.nhs.uk/sites/default/files/2019-12/Drug%20Tariff%20January%202020.pdf
7. National Institute for Health and Care Excellence. NICE guideline [NG 131]. Prostate cancer: diagnosis and management. Published May 2019. Available at https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133 Accessed 14/09/19.

8. NICE Evidence Summary. Prostate cancer: triptorelin (Decapeptyl® SR). New medicine [ESNM30]. Jan 2014. Accessed on 19/08/2019 via https://www.nice.org.uk/advice/esnm30/chapter/Key-points-from-the-evidence
9. PrescQIPP. Bulletin 257. Luteinising hormone-releasing hormone (LHRH) agonists in prostate cancer. April 2020.
10. Summary of Product Characteristics. Zoladex® 3.6 mg implant. AstraZeneca UK Ltd. Last updated 24/01/2017. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/1543/smpc
11. Summary of Product Characteristics. Zoladex LA® 10.8 mg implant. AstraZeneca UK Ltd. Last updated 24/01/2017. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/1567/smpc
12. Summary of Product Characteristics. Prostap® SR DCS 3.75 mg. Takeda UK Ltd. Last updated 11/05/2020. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/4650/smpc
13. Summary of Product Characteristics. Prostap® 3 DCS 11.25 mg. Takeda UK Ltd. Last updated 11/05/2020. Accessed on 19/08/2020 via https://www.medicines.org.uk/emc/product/4651/smpc
14. Personal communication Dr. Prabir Chakraborti, Consultant Oncologist, Stoke Mandeville Hospital, 7th May 2020.
15. Gonadotropin-releasing hormone (GnRH) analogues in Prostate Cancer guidelines, Oxfordshire clinical commissioning group, updated July 2017.
16. British National Formulary accessed online https://bnf.nice.org.uk/
17. Personal communication with Dr. P. Chakraborti, Uro-oncology Consultant, Buckinghamshire Healthcare NHS Trust, September 9th 2020.

Title of Guideline	Gonadorelin Analogues (GnRHa): Triptorelin, Goserelin and Leuprorelin for Prostate Cancer - Amber Recommendation Guideline
Guideline Number	789FM
Version	1
Effective Date	November 2020
Review Date	November 2023
Original Version Produced	February 2011 – original number 791FM (withdrawn 19/2/2020)
Equality Impact Assessment	5th October 2020
Approvals:	
Medicines Value Group	24th September 2020
Medicines Check (Pharmacy)	24th September 2020
Oncology and Haematology Clinical Governance	14th October 2020
Clinical Guidelines Group	20th October 2020
Author/s	Dr Prabir Chakraborti, Consultant Oncologist Maire Stapleton, Formulary Manager, BHT Roshni Kotecha, Medicines Optimisation Pharmacist, Bucks CCG
SDU(s)/Department(s) responsible for updating the guideline	Oncology, Urology, Pharmacy
Uploaded to Intranet	6th November 2020
Buckinghamshire Healthcare NHS Trust/Buckinghamshire Clinical Commissioning Group	

Appendix 1. GnRHa licensed indications for the treatment of prostate cancer

Indication	Goserelin^	Leuprorelin^	Triptorelin^
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	✓	✓	✓
As **neo-adjuvant** 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.	✓	✓	✓

^ Goserelin Zoladex® 3.6 mg, Zoladex® LA 10.8 mg
Leuprorelin Prostap® SR DCS 3.75 mg, Prostap® 3 DCS 11.25 mg
Triptorelin Decapeptyl SR 3 mg, 11.25 mg, 22.5 mg

Appendix 2. GnRHa doses, frequency and costs for the treatment of prostate cancer [1-4, 6, 10-13]

Drug	Goserelin		Leuprorelin		Triptorelin		
Brand and strength	Zoladex 3.6 mg	Zoladex LA 10.8 mg	Prostap SR DCS 3.75 mg	Prostap 3 DCS 11.25 mg	Decapeptyl SR 3 mg	Decapeptyl SR 11.25 mg	Decapeptyl SR 22.5 mg
Dosing interval	4-weekly	12-weekly	Monthly	3-monthly	4-weekly	3-monthly	6-monthly
Dosage form	Implant PFS	Implant PFS	Powder and Solvent PFS	Powder and Solvent PFS	Powder and Solvent PFS	Powder and Solvent PFS	Powder and Solvent PFS
Injection route	SC	SC	SC or IM	SC	IM	IM	IM
Needle size	16 gauge	14 gauge	23 gauge	23 gauge	20 gauge	20 gauge	20 gauge
Needle safety device	Yes	Yes	Yes	Yes	No	No	No
Cost per annum **Drug Tariff January 20**	£910	£1010.5	£903	£903	£897	£828	£818