***Amber with Guidance**= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

Barnsley Hospital NHS NHS Foundation Trust | South West Yorkshire Partnership NHS NHS Foundation Trust | NHS Barnsley Clinical Commissioning Group

Prostate Cancer: LHRH analogues / Cyproterone / Bicalutamide

<table>
<tr><td>Background Information</td><td>Metastatic cancer of the prostate usually responds to hormonal treatment aimed at androgen depletion. Treatment with gonadorelin analogues or anti-androgen drugs are often used.</td></tr>
<tr><td>BNF therapeutic class</td><td>6.6 Gonadotrophin responsive conditions and 8.4 Hormone responsive malignancy</td></tr>
<tr><td>Indication</td><td>LHRH analogues
<table>
<tr><th>Prescribe within their product licence wherever possible.</th><th>Goserelin (Zoladex®)</th><th>Leuprorelin (Prostap®)</th><th>Triptorelin (Decapeptyl®)</th><th>Triptorelin (Gonapeptyl®)</th></tr>
<tr><td>Metastatic prostate cancer</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Locally advanced prostate cancer</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Adjuvant to radiotherapy</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td></tr>
<tr><td>Neo-adjuvant to radiotherapy</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td></tr>
<tr><td>Adjuvant to surgery</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td></tr>
<tr><td>Neo-adjuvant to surgery</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
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Cyproterone
• Prevention of flare with initial gonadorelin analogue therapy (short term)
• Long-term palliative therapy where gonadorelin analogues or orchidectomy contra-indicated, not tolerated, or where oral therapy preferred.
• Hot flushes with gonadorelin analogue therapy or after orchidectomy

Bicalutamide
• Locally advanced prostate cancer.
• Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate
• Advanced prostate cancer, in combination with gonadorelin analogue or surgical castration.</td></tr>
<tr><td>Dosage and administration</td><td>• Triptorelin (Decapeptyl SR®) injection m/r 3mg vial (with diluent): by intramuscular injection, 3mg every 4 weeks.
• Triptorelin (Decapeptyl SR®) injection m/r 11.25mg vial (with diluent): by intramuscular injection, 11.25mg every 3 months.
• Triptorelin (Decapeptyl SR®) injection m/r 22.5mg vial (with diluent): by intramuscular injection, 22.5mg every every 6 months.
• Triptorelin (Gonapeptyl Depot®) prefilled syringe 3.75mg: by subcutaneous or by intramuscular injection 3.75mg every 4 weeks
• Leuprorelin (Prostap SR DCS®) acetate prefilled syringe 3.75mg: by subcutaneous or by intramuscular injection 3.75mg every 4 weeks.
• Leuprorelin (Prostap 3 DCS®) acetate prefilled syringe 11.25mg: by subcutaneous injection 11.25mg every three months.
• Goserelin (Zoladex®) prefilled syringe 3.6mg: by subcutaneous injection 3.6mg every 4 weeks.</td></tr>
</table>

	• **Goserelin (ZoladexLA®)** *prefilled syringe 10.8mg by subcutaneous injection:* 10.8mg subcutaneously every 3 months. **Bicalutamide** • Locally advanced prostate cancer at high risk of disease progression, 150 mg once daily • Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate, 150 mg once daily Advanced prostate cancer, in combination with gonadorelin analogue or surgical castration, 50 mg once daily (started at the same time as surgical castration or at least 3 days before gonadorelin therapy) **Cyproterone** • Prevention of flare with initial gonadorelin analogue therapy, 200 mg daily in 2–3 divided doses for 5–7 days before initiation of gonadorelin analogue, followed by 200 mg daily in 2–3 divided doses for 3–4 weeks after initiation of gonadorelin analogue; max. 300 mg daily • Long-term palliative therapy where gonadorelin analogues or orchidectomy contra-indicated, not tolerated, or where oral therapy preferred, 200–300 mg daily in 2–3 divided doses • Hot flushes with gonadorelin analogue therapy or after orchidectomy, initially 50 mg daily, adjusted according to response to 50–150 mg daily in 1–3 divided doses
Cautions and Contraindication	**<u>LHRH analogues</u>** **Contraindications** • Known severe hypersensitivity to the active substance or to any of the excipients of this product. • Pregnancy and lactation • Use in children **Cautions** • When LHRH/GnRH analogues are used in the treatment of prostate cancer, accelerated growth of the malignancy may occur during the first 3 weeks after the first injection. This possibility should be blocked by the use of an anti-androgen such as cyproterone acetate 100mg three times daily or flutamide 250mg three times daily given for 4 days prior to commencement of treatment and three weeks after commencement of treatment. • Men with urinary obstruction or metastatic vertebral lesions should be closely supervised for the first few weeks of therapy. These patients should be checked especially if they are at risk of ureteric obstruction or spinal cord compression that they can tolerate an anti-androgen before the first dose of an LH-RH analogue is administered. All patients should be given prophylactic treatment with antiandrogens at the start of therapy. • Diabetic patients may require frequent monitoring of blood glucose levels. • The use of LHRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an LHRH agonist may reduce bone mineral loss. Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with anticonvulsants or corticosteroids, family history of osteoporosis). • Mood changes, including depression have been reported. Patients with known depression should be monitored carefully. • Androgen deprivation therapy may prolong the QT interval - In patients with a history of, or risk factors for, QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating an LHRH analogue. **<u>Bicalutamide</u>** **Contraindications** • Youths under 18 years • Co-administration of terfendadine, astemizole or cisapride

	Cautions • To be used in caution in patients with moderate to severe hepatic impairment, consider periodic liver function tests. **Cyproterone** **Contra-indications:** (do not apply in prostate cancer), severe diabetes (with vascular changes), sickle-cell anaemia, liver-disease including Dubin-Johnson and Rotor syndromes, previous or existing liver tumours, malignant diseases or wasting diseases, meningioma or history of meningioma, severe depression, history of thromboembolic disorders; youths under 18 years (may arrest bone maturation and testicular development) **Cautions:** Diabetes mellitus, in prostate cancer: severe depression or sickle cell anaemia, ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known). The occurrences of thromboembolic events, meningiomas and direct hepatic toxicity have been reported.
Adverse Drug Reactions	**LHRH analogues - In general** Tumour flare. Skin reactions and local reactions including bruising at the injection site. Hotflushes, decrease in libido, impotence, breast swelling and tenderness have also been reported. Initially prostate cancer patients may experience a temporary increase in bone pain. *Goserelin* Adverse events which have been reported include hypersensitivity reactions, arthralgia, skin rashes, and changes in blood pressure. These changes are usually transient. Weight gain, mood change, gynaecomastia, bone pain, headache, migraine, changes in blood lipids and hypotension or hypertension. Myocardial infarction and abnormal blood pressure. *Leuprorelin* Include peripheral oedema, fatigue, nausea, headaches (occasionally severe), arthralgia, dizziness, insomnia, visual disturbances, weight change, hot flushes, hyperhidrosis and bone pain. **Bicalutamide** Anaemia, decreased appetite, decreased libido, depression, dizziness, somnolence, hot flushes, abdominal pain, constipation, dyspepsia, flatulence, nausea, hepatotoxicity, jaundice, hypertransaminasemia, rash, alopecia, hirsuitism/hair re-growth, dry skin, pruritis, haematuria, gynaecomastia and breast tenderness. Erectile dysfunction, asthenia, chest pain, oedema and weight gain. Uncommon: interstitial lung disease, hypersensitivity, angioedema and urticarial. **Cyproterone** Fatigue and lassitude, breathlessness, weight changes, depressive moods, restlessness (temporary) gynaecomastia (rarely leading to galactorrhoea and benign breast nodules); rash, osteoporosis; inhibition of spermatogenesis; direct hepatotoxicity reported (including jaundice, hepatitis and hepatic failure. Fatalities reported at dosages of 100 mg and above, usually in men treated for advanced prostate cancer), sperm count and volume of ejaculate are reduced.
Monitoring	**LHRH analogues** This will generally be the responsibility of the consultant but GPs should be aware of the "flare phenomenon" which may produce hypercalcaemia and other problems within the first three weeks of initiation of treatment in a patient with hormone dependant malignancy. Prostate specific antigen (PSA) should be measured at 3-6 monthly intervals. Referral to secondary care is indicated in the event of a patient presenting to their GP with signs of clinical deterioration e.g. spinal cord compression or adverse events that have led the GP to terminate treatment. Blood pressure should be checked every 3 months. More frequent BP check may be required if it is outside the normal range. Monitor liver function for patients on leuprorelin. **Bicalutamide** Periodic liver function testing should be considered due to the possibility of hepatic changes.

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	Cyproterone • Monitor blood counts initially and throughout treatment. • Monitor adrenocortical function regulary • Monitor hepatic function regularly- liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of heptatotoxicity occur.
Interactions	*Triptorelin* Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of LHRH receptors in the pituitary. *Goserelin* There are no documented drug interactions for Goserelin in the BNF or SPC. *Leuprorelin* There are no documented drug interactions for Leuprorelin in the BNF or SPC. *Bicalutamide* • Possibly enhanced anti-coagulant effect of coumarins • Terfenadine, astemizole and cisapride • Ciclosporin and calcium channel blockers - Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of bicalutamide therapy. • Caution should be exercised when prescribing bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole *Cyproterone* • Antidiabetics: The requirement for oral antidiabetics or insulin can change. • Cyproterone acetate is metabolised by CYP3A4, therefore may interact with ketoconazole, intraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4. • Inducers of CYP3A4 such as rifampicin, phenytoin and products containing St. John's wort may reduce the levels of cyproterone acetate. • Statins: The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMG-CoA inhibitors (statins) which are primarily metabolised by CYP3A4 are co-administered with high therapeutic cyproterone acetate doses, since they share the same metabolic pathway.

Contact names and details

Contact Details	Telephone number	Email
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For information relating to administration training please contact Russell Dowde above.

References

- British National Formulary78 September 2019-March 2020
- Summary of Product Characteristics available at:

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- Zoladex® 3.6mg implant http://www.medicines.org.uk/EMC/medicine/7855/SPC/Zoladex+3.6mg+Implant/
- Zoladex LA® 10.8mg http://www.medicines.org.uk/EMC/medicine/8146/SPC/Zoladex+LA+10.8mg/
- Prostap® SR DCS 3.75mg https://www.medicines.org.uk/emc/product/4650
- Prostap® 3 DCS 11.25mg https://www.medicines.org.uk/emc/product/4651
- Decapeptyl® SR 3mg http://www.medicines.org.uk/EMC/medicine/868/SPC/Decapeptyl+SR+3mg/
- Decapeptyl® SR 11.25mg
- https://www.medicines.org.uk/emc/product/780/smpc780/smpc
- Gonapeptyl Depot® http://www.medicines.org.uk/EMC/medicine/12870/SPC/Gonapeptyl+Depot+3.75+mg/
- Bicalutamide https://www.medicines.org.uk/emc/product/2052/smpc
- Cyproterone. Cyprostat® http://www.medicines.org.uk/emc/medicine/20815

Development Process

This guideline was developed following an AMBER-G (Amber with guidance) classification status of LHRH/GnRH analogues, cyproterone and bicalutamide by the Barnsley Area Prescribing Committee in January 2015. This information has been updated and was ratified at the Area Prescribing Committee on 10th March 2021.