Prostate Cancer: LHRH analogues / Cyproterone / Bicalutamide

Background Information
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.

BNF therapeutic class
8.3.4.2 Gonadorelin analogues and gonadotrophin-releasing hormone antagonists

<table>
<thead>
<tr>
<th>Indication</th>
<th>LHRH analogues</th>
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<tbody>
<tr>
<td>Prescribe within their product licence wherever possible.</td>
<td><strong>Goserelin (Zoladex®)</strong></td>
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<tr>
<td>Metastatic prostate cancer</td>
<td>Yes</td>
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<tr>
<td>Locally advanced prostate cancer</td>
<td>Yes</td>
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<tr>
<td>Adjuvant to radiotherapy</td>
<td>Yes</td>
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<tr>
<td>Neo-adjuvant to radiotherapy</td>
<td>Yes</td>
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<tr>
<td>Adjuvant to surgery</td>
<td>Yes</td>
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<tr>
<td>Neo-adjuvant to surgery</td>
<td>No</td>
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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.

Dosage and administration
- **Triptorelin (Decapeptyl SR®)** injection m/r 4.2mg vial (with diluent): by intramuscular injection, 3mg every 4 weeks.
- **Triptorelin (Decapeptyl SR®)** injection m/r 15mg vial (with diluent): by intramuscular injection, 11.25mg every 3 months.
- **Triptorelin (Decapeptyl SR®)** injection m/r 28mg vial (with diluent): by intramuscular injection, 22.5mg 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 for 3 months.
- **Goserelin (ZoladexLA®)** prefilled syringe 10.8mg by subcutaneous injection: 10.8mg
**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.

<table>
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<th>Subcutaneously every 3 months.</th>
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**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**

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<th>LHRH analogues</th>
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**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 tds or flutamide 250mg tds 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.

**Bicalutamide**
**Cautions:** 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 or wasting diseases, menigioma or history of menignioma, severe depression, history of thromboembolic disorders; youths under 18 years (may arrest bone maturation and testicular development)
**Cautions:** Ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known); blood counts initially and throughout treatment; monitor hepatic function regularly (liver function tests should be performed before treatment) monitor adrenocortical function regularly; diabetes mellitus. Driving Fatigue and lassitude may impair performance of skilled tasks (e.g. driving).

### Adverse Drug Reactions

<table>
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<th>LHRH analogues - In general:</th>
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<tr>
<td>Tumour flare. Skin reactions and local reactions including bruising at the injection site. Hot flushes, decrease in libido, impotence, breast swelling and tenderness have also been reported. Initially prostate cancer patients may experience a temporary increase in bone pain.</td>
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</table>

#### 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 Headache (occasionally severe), Migraine, Changes in blood lipids and Hypotension or hypertension.

#### Leuprolelin

Include peripheral oedema, fatigue, nausea, headaches (occasionally severe), arthralgia, dizziness, insomnia, visual disturbances, weight change.

#### Bicalutamide|

Nausea, diarrhoea, cholestasis, jaundice; asthenia, weight gain; gynaecomastia, breast tenderness, hot flushes, impotence, decreased libido; anaemia; alopecia, dry skin, hirsutism, pruritus; less commonly vomiting, abdominal pain, dyspepsia, interstitial lung disease, pulmonary fibrosis, depression, haematuria, thrombocytopenia, hypersensitivity reactions including angioneurotic oedema and urticaria; rarely cardiovascular disorders (including angina, heart failure, and arrhythmias), and hepatic failure.

#### Cyproterone:

Fatigue and lassitude, breathlessness, weight changes, reduced sebum production (may clear acne), changes in hair pattern, gynaecomastia (rarely leading to galactorrhoea and benign breast nodules); rarely hypersensitivity reactions, rash and osteoporosis; inhibition of spermatogenesis; 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).

#### Monitoring

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<td>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.</td>
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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.

#### Bicalutamide

Periodic liver function testing should be considered due to the possibility of hepatic changes.

#### Cyproterone

Blood counts initially and throughout treatment. Monitor FBC and LFTs 6 monthly. Monitor hepatic function regularly - Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (fatalities reported at dosages of 100 mg and above, usually in men treated for advanced prostate cancer). Liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of hepatotoxicity occur—if confirmed cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease (in which case cyproterone should be continued only if the perceived benefit exceeds the risk) Monitor adrenocortical function regularly.
**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.

### 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, intracranzirole, 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

<table>
<thead>
<tr>
<th>Contact Details</th>
<th>Telephone number</th>
<th>Email</th>
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<tbody>
<tr>
<td>Russell Dowde (Urology nurse practitioner)</td>
<td>01226 432811</td>
<td><a href="mailto:russell.dowde@nhs.net">russell.dowde@nhs.net</a></td>
</tr>
<tr>
<td>Mr David Smith (Lead Consultant for Urology)</td>
<td></td>
<td><a href="mailto:david.smith3@nhs.net">david.smith3@nhs.net</a></td>
</tr>
<tr>
<td>Medicines Information</td>
<td>01226 432857</td>
<td><a href="mailto:gilliansmith2@nhs.net">gilliansmith2@nhs.net</a></td>
</tr>
</tbody>
</table>

For information relating to administration training please contact Russell Dowde above.

### References

- British National Formulary
- Summary of Product Characteristics available at:
  - Prostap® SR DCS 3.75mg [http://www.medicines.org.uk/EMC/medicine/2238/SPC/Prostap+SR/](http://www.medicines.org.uk/EMC/medicine/2238/SPC/Prostap+SR/)
**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.

- Gonapeptyl Depot®  

- Bicalutamide  
  [http://www.medicines.org.uk/emc/medicine/23322](http://www.medicines.org.uk/emc/medicine/23322)

- Cyproterone. Cyprostat®  

**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 subject to consultation and endorsement by the Consultant Urologist Dr David Smith and was ratified at the Area Prescribing Committee on 13th May 2015 and the LMC on 9th June 2015.