SHARED CARE GUIDELINE

Homerton University Hospital NHS Foundation Trust

City and Hackney Teaching Primary Care Trust

NON – STEROIDAL ANTI-ANDROGEN THERAPY FOR THE TREATMENT OF PROSTATE CANCER

INTRODUCTION

Metastatic cancer of the prostate usually responds to hormonal treatments aimed at androgen depletion. The non- steroidal anti–androgens inhibit androgen uptake and or nuclear binding of androgen in target tissues.

The anti-androgens include flutamide and bicalutamide, they have several indications it is therefore important to determine specifically the exact indication and the intended mode of use.

INDICATIONS

FLUTAMIDE	BICALUTAMIDE
• As monotherapy in the treatment of advanced prostate carcinoma	• As monotherapy for locally advanced prostate cancer.
• Initial treatment in combination with a Luteinizing hormone releasing hormone (LHRH) agonist therapy	• Treatment of advanced prostate cancer in combination with LHRH analogue therapy
• As adjunctive therapy in patients already receiving LHRH agonist therapy (Maximum androgen blockade). This is an unlicensed indication.	
• In surgically castrated patients and in the treatment of patients who have not responded to other forms of hormonal manipulation or in patients who cannot tolerate such treatments.	

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DOSE AND ADMINISTRATION

FLUTAMIDE	BICALUTAMIDE
• One 250mg tablet orally three times a day at 8 hour intervals	• As monotherapy, one 150mg tablet orally once a day
	• As adjunctive therapy one 50mg tablet orally once a day

Anti-androgens when used as an initial treatment with an LHRH agonist therapy reduces the incidence and severity of the LHRH agonist flare. In susceptible patients this tumour flare may cause spinal cord compression, ureteric obstruction or increased bone pain. It is therefore recommended that the anti-androgens should be started 7 days before the LHRH agonist and continued for a total of at least two weeks.

Neoadjuvant therapy: for low risk patients

Anti-androgen for three months with hormonal therapy, 1 month during radiation therapy and then followed by two months after radiation therapy.

(Dose as recommended by the oncologist)

Adjuvant therapy: for high - risk patients

Anti-androgens with LHRH for three months before radiation therapy and continued through the course of radiation therapy and then continued thereafter for three years.

(Dose as recommended by the oncologist)

DOSE ADJUSTMENTS IN LIVER INSUFFICIENCY

Non–steroidal anti- androgens may be hepatotoxic and in patients with impaired liver function, long term treatment with the anti- androgens should only be administered after careful assessment of the individual benefits and risks. Regular liver function test should be carried out (once every month).

CONTRA-INDICATIONS

- The anti-androgens are contra-indicated in patients who have moderate to severe hepatic impairment or who are hypersensitive to the drug.
- Contra-indicated in children and females.

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SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- The anti-androgens may be hepatotoxic and this may rarely cause transaminase abnormalities, cholestatic jaundice, hepatic necrosis and hepatic encephalopathy.
- Flutamide and Bicalutamide should not be initiated in patients with serum transaminase levels exceeding 2-3 times the upper limit of normal (AST 5 – 35 u/l, ALT 7 – 24u/l)
- Bicalutamide is extensively metabolised in the liver and data suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide therefore Bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

INTERACTIONS

Flutamide:

- Prothrombin time should be closely monitored in patients receiving long- term warfarin therapy as prothrombin time is increased on initiation of flutamide**.**
- Dose adjustment of warfarin may be necessary when flutamide is administered concomitantly with warfarin.

Bicalutamide:

- Concomitant use of terfenadine, astemizole and cisapride is contraindicated as bicalutamide is an inhibitor of the cytochrome P450 enzyme system
- Cimetidine and ketoconazole may increase Bicalutamide levels by inhibiting drug oxidation therefore they should be prescribed with caution.
- Prothrombin time should be closely monitored in patients receiving long- term warfarin therapy as prothrombin time is increased due to the displacement of warfarin by bicalutamide from its protein binding sites.

SIDE- EFFECTS

- Gynecomastia and /or breast tenderness, sometimes accompanied by galactorrhea
- Transient abnormal liver function, hepatitis, cholestatic jaundice, hepatic encephalopathy and hepatic necrosis
- Less frequent adverse reactions such as diarrhoea, nausea, vomiting, increased appetite, insomnia and tiredness
- Reduced sperm count, decreased libido, upset stomach, constipation and lupus like syndrome

See BNF and Summary of Product Characteristics for comprehensive list.

MONITORING STANDARDS FOR ANTI-ANDROGENS

The following standards have been agreed for the monitoring:

Pre - treatment	During treatment
• **Baseline Liver function tests**	• **Liver function tests should be performed monthly for the first four months then 6 monthly thereafter and at the first sign or symptom of liver disorder (i.**e pruritis, dark urine, persistent anorexia, jaundice, abdominal pain and unexplained influenza – like symptoms**)**
• **Exclude all contraindications**	

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EVENTS AND ACTION

Laboratory Events	Normal Range	Values	Action
• Elevation in liver enzymes (AST, ALT)	AST (5 – 35 U/L) ALT (7 – 24 U/L)	>2x ULN (upper limit of normal)	**Discontinue antiandrogen and seek specialist advice**
• Bilirubin	Less than 17μmol/l	>ULN	**Discontinue antiandrogen and seek specialist advice**

REMEMBER if unsure at any point: Contact the various Specialists and or Specialist Nurse/ Nurse Practitioner via the Homerton Hospital switchboard on 020 8510 5555.