Abiraterone and Prednisolone

Indication
Treatment of advanced metastatic castration resistant prostate cancer (mCRPC) for patients who have progressed on or after a docetaxel containing chemotherapy regimen.
(NICE TA259)

Treatment of advanced metastatic castration resistant prostate cancer (mCRPC) for patients who are asymptomatic or mildly symptomatic where chemotherapy is not yet indicated.
(NICE TA387)

ICD-10 codes
Codes with a prefix C61

Regimen details

Drug	Dose	Route
Abiraterone acetate	1000mg OD	PO
Prednisolone	5mg BD or 10mg OM	PO

Cycle frequency
Once daily until disease progression or unacceptable toxicity.

Number of cycles
As above

Administration
Abiraterone is available as 500mg tablets.

Abiraterone should be taken without food, at least one hour before or two hours after eating. Tablets should be swallowed whole with water and not broken or crushed.

In the event of a missed dose, treatment should be omitted and continued the next day at the usual dose.

A daily dose of prednisolone must be administered with abiraterone. On discontinuation of abiraterone the prednisolone dose should be slowly tapered down and patients should be monitored for adrenal insufficiency.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (no routine antiemetics are required).

Additional supportive medication
Nil

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
Potassium	14 days
LFTs	14 days
Blood pressure (BP)	Must be controlled before initiating treatment
PSA	Baseline
Glucose	Baseline
HbA1c	Baseline

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Monthly
U+E (including creatinine)	Monthly
Potassium*	Monthly
LFTs	Every 2 weeks for the first 3 months, monthly thereafter
Blood pressure	Monthly
PSA	Monthly or 2 monthly as indicated
Glucose	As clinically indicated

*Consider maintaining serum potassium levels ≥ 4.0 mmol/L

Periodic monitoring of ECG if relevant cardiac history.
Monthly assessment for fluid retention (2 weekly if significant risk of congestive cardiac failure).

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Creatinine clearance (CrCl)	≥ 30ml/min
Bilirubin	≤ ULN
AST/ALT	≤ 5 x ULN

Dose modifications

- **Haematological toxicity**

Abiraterone is not myelosuppressive and so treatment may continue in the presence of myelosuppression.

- **Renal impairment**

CrCl (mL/min)	**Abiraterone dose**
≥ 30	100%
< 30	No experience of use in patients with CrCl < 30mL/min – use with caution

- **Hepatic impairment**

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A. Initiation of abiraterone and prednisolone should be avoided in patients with moderate to severe pre-existing hepatic impairment (Child-Pugh Class B and C).

For patients who develop hepatotoxicity during treatment (ALT increases >5 x ULN), treatment with abiraterone should be withheld immediately.

ALT (x ULN)	Abiraterone dose
>5-19 x ULN	Withhold until ALT returned to baseline then reduce dose to 500mg OD
≥ 20 x ULN	Permanently discontinue treatment

For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued.

- **Other toxicities**

Hypertension:
Blood pressure must be controlled prior to commencing treatment.

Blood pressure	Abiraterone dose
Diastolic increase >20mmHg above baseline OR BP >150/100mmHg	100% Initiate or adjust antihypertensive therapy Monitor BP
BP >180/110mmHg	Withhold until BP controlled

Hypokalaemia:
Hypokalaemia must be corrected prior to commencing treatment.

Potassium (mmol/L)	Abiraterone dose
≥ 3.0	100%
<3.0	Withhold until within normal limits*

*Manage according to local guidelines

Cardiac Disorders:
There is no clinical experience with abiraterone in patients with clinically significant heart disease. Abiraterone should be avoided where possible.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cardiac failure
Arrhythmias
Hepatotoxicity
Adrenal insufficiency
Myopathy
Allergic alveolitis

- **Frequently occurring side effects**

Peripheral oedema
Fluid retention
Hypokalaemia
Hypertension
Urinary tract infection
Diarrhoea
Hyperglycaemia

- **Other side effects**

Fractures
Rash

Significant drug interactions – for full details consult product literature/ reference texts

Medicinal products activated by or metabolised by CYP2D6 (e.g**.** metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecanide, codeine, oxycodone and tramadol): caution is advised when abiraterone acetate is administered with medicinal products activated or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Codeine, oxycodone and tramadol are metabolised via CYP2D6 to their active metabolites and so abiraterone may have an (as yet unknown) effect on patient's analgesic requirements if treated with these agents.

Strong inhibitors and inducers of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or **inducers** (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital): avoid or use with caution.

Spironolactone: binds to the androgen receptors and may increase PSA levels. Concomitant use not recommended.

Additional comments

Abiraterone must be administered with oral prednisolone 10mg daily. Blood glucose levels should be measured regularly in patients due to the steroid use. Abiraterone acetate may cause hypertension, hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions.
Contraception: It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method.

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 259 accessed 1 May 2014 via www.nice.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 387 accessed 1 May 2017 via www.nice.org.uk
- De Bono JS et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. A randomised phase 3 placebo-controlled multicentre trial *N Engl J Med* 2011 364;1995-2005
- Summary of Product Characteristics Abiraterone (Janssen- Cilag) accessed 2 May 2018 via www.medicines.org.uk

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Date: 11 December 2014 reviewed May 2018