Abiraterone and Prednisolone Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Abiraterone is indicated in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.	C61	00103a	CDS
Treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated	C61	00103b	CDS

**If the reimbursement status is not defined[1], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Abiraterone is administered as a single oral daily dose until disease progression or unacceptable toxicity develops (1 cycle = 28 days).

Androgen ablative therapy (e.g. LHRH agonist, LHRH antagonist) should be maintained.

Drug	Dose	Route	Cycle
Abiraterone	1000mg daily	PO without food at the same time each day[1]. Tablets should be swallowed whole with water.	Continuous therapy
Prednisone or Prednisolone	10mg daily or 5mg BD	PO with food	Continuous therapy
In the event of a missed daily dose of either abiraterone, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.			
[1]Abiraterone should be taken at least one hour before or at least two hours after eating			

ELIGIBILTY:

- Indications as above
- ECOG status 0-2
- Life expectancy > 3 months
- Bilirubin < 1.5 x ULN, AST/ALT < 2.5 x ULN, Alkaline Phosphatase < 6 x ULN
- Creatinine < 1.5 x ULN
- Serum potassium > 3.5mmol/L

EXCLUSIONS:

- Hypersensitivity to abiraterone or any of the excipients
- Uncontrolled hypertension (systolic blood pressure >160mmHg or diastolic > 95mmHg)
- Severe hepatic impairment
- Active or symptomatic viral hepatitis
- Clinically significant heart disease (LVEF < 50% at baseline)
- History of adrenal dysfunction
- Patients with visceral metastases
- Patients who have received > 7days of ketoconazole

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose, blood pressure
- ECG if clinically indicated or if history of cardiac problems

Regular tests:

- FBC, renal and liver profile, glucose and blood pressure every 2 weeks for cycles 1-3 and every 4 weeks thereafter
- ECG if clinically indicated or if history of cardiac problems

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Renal and Hepatic Impairment:

Table 1: Dose modification of abiraterone in renal and hepatic impairment

Renal Impairment	Hepatic Impairment			
No dose modification is necessary in patients with renal impairment. However there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.	**Bilirubin**		**AST and/or ALT**	**Dose**
	1.5 – 3 x ULN	and	2.5 – 5 x ULN	100% Monitor liver tests at least weekly until grade 1 (Bilirubin < 1.5 x ULN, AST/ALT < 2.5 x ULN).
	> 3 x ULN	or	> 5 x ULN	**Hold abiraterone**. Treatment following return of liver function tests to the patient's baseline should be reinitiated with a dose of 500mg once daily. 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 500mg daily, treatment should be discontinued.
	If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.			

Management of adverse events:

Hypokalemia Management:

Hypokalemia has been observed and should be aggressively managed.

Serum potassium should be monitored closely in patients who develop hypokalemia.

Table 2: Management of Hypokalemia

Serum K+ (mmol/L)	Grade of Hypokalemia	Action	Further Action or Maintenance
Low K+ or History of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations.	Titrate dose to maintain potassium > 3.5 mmol/L and < 5.0 mmol/L (> 4.0 mmol/L recommended).
< 3.5 – 3.0	Grade 1	Initiate oral or IV potassium supplementation. Consider monitoring magnesium and replacement if needed.	
< 3.5 – 3.0 Symptomatic	Grade 2	Withhold abiraterone until potassium corrected. Initiate oral or IV potassium supplementation. Consider monitoring magnesium and replacement if needed.	
< 3.0 – 2.5	Grade 3	Withhold abiraterone until potassium corrected. Initiate oral or IV potassium and consider cardiac monitoring in appropriate patients. Consider monitoring magnesium and replacement if needed.	
< 2.5	Grade 4		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS:
Not usually required

OTHER SUPPORTIVE CARE:
Patients who stop abiraterone may require a gradual withdrawal of the prednisolone.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Fluid retention:** Fluid retention can occur due to mineralocorticoid excess caused by compensatory adrenocorticotropic hormone (ACTH) drive. The administration of prednisolone will help reduce incidence and severity of fluid retention.
- **Hypertension:** Patients with hypertension should exercise caution while on abiraterone. Rigorous treatment of blood pressure is necessary, since abiraterone can cause a rapid onset of high blood pressure. Blood pressure will need to be monitored once every 2 weeks for the first three months of abiraterone therapy.
- For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with abiraterone should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline
- **Cardiac Function:** Abiraterone should be used with caution in patients with a history of cardiovascular disease. QT prolongation has been observed in patients experiencing hypokalaemia in association with abiraterone treatment. Cardiac function should be assessed as clinically indicated and the discontinuation of abiraterone treatment considered if there is a clinically significant decrease in cardiac function.
- **Hepatic Dysfunction:** Abiraterone undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST and ALT) may occur during the first 3 months after starting treatment so a more frequent monitoring of liver function tests is required (every 2 weeks in the first three months and monthly thereafter). There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome
- **Bone density.** Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of abiraterone in combination with a glucocorticoid could increase this effect.
- **Hyperglycaemia:** The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in diabetic patients.

DRUG INTERACTIONS:

- The clearance of drugs metabolized by CYP2D6 may be decreased as abiraterone is a strong inhibitor of CYP2D6. Dose reduction should be considered especially for drugs with a narrow therapeutic index.
- Risk of drug interactions causing decreased concentrations of abiraterone with CYP3A4 inducers.

- Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Abiraterone – L02BX03

REFERENCES:

1. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-48.
2. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.
3. Logothetis C, de Bono JS, Molina A et al. Effect of abiraterone acetate on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer post docetaxel: Results from the COU-AA-301 phase III study. J Clin Oncol 2011:29; (suppl; abstr 4520).
4. Zytiga ®Summary of Product Characteristics Accessed April 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf

Version	Date	Amendment	Approved By
1	20/12/2014		Dr Ray McDermott
2	3/3/2015	Updated Tests	Dr Maccon Keane
3	26/3/2015	Addition of new indication	Dr Derek Power, Dr Maccon Keane
4	01/10/2015	Updated Adverse Effects and Drug Interactions	Dr Maccon Keane
5	13/4/2016	Updated dosing in hepatic impairment and hepatic dysfunction under Adverse Events	Dr Maccon Keane
6	18/04/2018	Updated with new Regimen Template and updated Adverse Events	Prof Maccon Keane
7	27/03/2019	Updated administration details for abiraterone	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/