Abiraterone 1000mg and Prednisolone 5mg Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Abiraterone is indicated with prednisone or prednisolone for: the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)	C61	00577a	Reimbursement not approved

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 during treatment in patients not surgically castrated.

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	5mg daily	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			

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Patients are required to have at least two of the three following high-risk factors associated with poor prognosis:
  - Gleason score ≥8
  - ≥Three bone lesions
  - Presence of measurable visceral metastasis. (RECIST 1.1)
- Adequate hematologic, hepatic, and renal function

EXCLUSIONS:

- Hypersensitivity to abiraterone or any of the excipients
- Known brain metastasis
- Uncontrolled hypertension (systolic blood pressure >160mmHg or diastolic > 95mmHg)
- Active or symptomatic viral hepatitis or chronic liver disease
- Severe hepatic impairment
- History of adrenal dysfunction
- Clinically significant heart disease (LVEF <50% at baseline)
- Abiraterone with prednisone or prednisolone is contraindicated in combination with Ra-223

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:

Table 2: Dose Modification of Abiraterone for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities	Withhold treatment 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

Hypokalemia Management:

Patients with pre-existing hypokalaemia or those that develop hypokalaemia while treated with abiraterone, consider maintaining the patient's potassium level at ≥4.0mM.

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.
- **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 significcnt 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.
- **Anaemia** may occur in men with metastatic prostate cancer including those undergoing treatment with abiraterone.
- **Sexual dysfunction** may occur in men with metastatic prostate cancer including those undergoing treatment with abiraterone.
- **Skeletal muscle effects:** Cases of myopathy and rhabdomyolysis have been reported in patients treated with abiraterone. Most cases developed within the first 6 months of treatment and recovered after abiraterone withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

DRUG INTERACTIONS:

- Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8. Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6 or CYP2C8, particularly with medicinal products that have a narrow therapeutic index.
- 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 torsades 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.
- Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with abiraterone is not recommended.
- Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [Hypericum perforatum]) during treatment are to be avoided, unless there is no therapeutic alternative.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Abiraterone – L02BX03

REFERENCES:

1. Fizazi K. et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017 Jul 27;377(4):352-360. doi: 10.1056/NEJMoa1704174. Epub 2017 Jun 4. Including supplementary material.
2. Fizazi K. et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019 May;20(5):686-700. doi: 10.1016/S1470-2045(19)30082-8.
3. Abiraterone SmPC. EMA. Accessed Dec 2020.Last updated: 23/07/2020 Available at: https://www.ema.europa.eu/en/documents/product-information/zytiga-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	08/01/2020		Prof Maccon Keane
2	06/01/2021	Amended adverse effects	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.