Enzalutamide Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.	C61	00233a	CDS
Treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated	C61	00233b	CDS
The treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)	C61	00233c	Reimbursement not approved[i]

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.

Enzalutamide is administered as a single oral daily dose until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Enzalutamide	160mg once daily	PO	Continuous
The capsules should not be chewed, dissolved or opened but should be swallowed whole with water, and can be taken with or without food.			
If a dose is missed at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.			
Medical castration with an LHRH analogue should be continued during treatment of patients not surgically castrated.			

ELIGIBILITY:

- Indications as above
- ECOG status
  - Metastatic CRPC: 0-2
  - Non-metastatic CRPC : 0-1

EXCLUSIONS:

- Hypersensitivity to enzalutamide or any of the excipients
- Severe hepatic impairment
- Uncontrolled hypertension
- Patients suffering from fructose intolerance

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- Blood pressure, ECG in patients at risk of QT prolongation.
- INR for patients on warfarin.

Regular tests:

- 4 weekly FBC, renal and liver profile as clinically indicated
- Blood pressure as clinically indicated
- ECG, creatinine as clinically indicated
- Weekly INR tests if patient is on warfarin until stable warfarin dose established

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 enzalutamide in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment or end-stage renal disease.	No dose modification is necessary for patients with mild, moderate or severe hepatic impairment (Child Pugh Class A, B or C respectively.) An increased drug half-life has however been observed in patients with severe hepatic impairment.

Management of adverse events:

Table 2: Dose modification of enzalutamide for Adverse Events

Adverse reactions	Recommended dose modification
Intolerable or ≥ Grade 3	Interrupt therapy for 7 days or until symptoms resolved to ≤ grade 2, then treatment may be resumed at the same dose or a reduced dose (120mg or 80mg) if warranted.
Seizures	Discontinue
Severe hypertension	Interrupt therapy until hypertension has been controlled.
Posterior reversible encephalopathy syndrome (PRES)	Discontinue

Concomitant use with strong CYP2C8 inhibitors:

- The concomitant use of strong CYP2C8 inhibitors should be avoided if possible.
- If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80mg once daily.
- If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitors.

SUPPORTIVE CARE:

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

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Enzalutamide may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizures have been reported. Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Risk of seizure**: Enzalutamide is associated with an increased risk of seizure, with a greater risk of seizure at daily doses >160mg. Caution is advised in administering the drug to patients with a history of seizure or other predisposing factors.
- **Posterior reversible encephalopathy syndrome (PRES):** There have been rare reports of PRES in patients receiving enzalutamide treatment. Discontinuation of enzalutamide in patients who develop PRES is recommended.
- **Concomitant use with other medicinal products**:
  - Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment.

- Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.
- Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistant protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).
- The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier.
- In consideration of the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

- **Cardiovascular disease**: Exercise caution in patients with significant cardiovascular disease, history of hypertension or QT prolongation, risk factors for torsades de pointes, or on medications known for QT prolongation. Androgen ablation therapy may prolong the QT interval. Enzalutamide is associated with increased blood pressure in approximately 7% of patients. Hypertension rarely leads to discontinuation or dose modification but may require antihypertensive treatment. Temporary suspension of enzalutamide is recommended in patients with severe hypertension (>200mmHg systolic or >110mgHg diastolic). Treatment with enzalutamide may be resumed once hypertension is controlled.
- **Hypersensitivity reactions**: Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide. Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

DRUG INTERACTIONS:

- CYP2C8 inhibitors and inducers affect plasma concentrations of enzalutamide and should be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80mg once daily.
- Current drug interaction databases should be consulted for more information

REFERENCES:

1. Beer TM, Armstrong AJ et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424-33
2. Scher HI, Fizazi K et al. Increased survival with Enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367:1187-1197.
3. Enzalutamide (Xtandi®) SmPC EMA. Last updated: 23/06/2021. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf

4. Hussain M et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474. doi: 10.1056/NEJMoa1800536.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	10/1/2015		Dr Miriam O Connor
2	01/01/2016	Inclusion of second licensed and funded indication 00233b	Dr Ray McDermott
3	28/06/2016	Amended requirement for 4 weekly tests to be done as clinically indicated. Deleted requirement for blood pressure to be checked every 2 weeks for first 12 weeks and then every 4 weeks	Dr Ray McDermott
4	20/06/2018	Updated with new NCCP regimen template Clarified dosing with concomitant use with strong CYP2C8 inhibitors	Prof Maccon Keane
5	04/09/2019	Inclusion of new indication	Prof Maccon Keane
6	28/07/2021	Reviewed. Added to regular tests and Table 2 (PRES). Updated adverse effects (enzymes induction and hypersensitivity)	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html for the most up to date reimbursement approvals.

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes