ENZALUTAMIDE (XTANDI®) for Castrate-resistant Metastatic Prostate Cancer

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Cycle length	Drug	Daily Dose	Route	Schedule
Days 1 to 28	4 weeks	**Enzalutamide**	160mg	Oral	Once daily

Enzalutamide is available as 40mg capsules, which should be swallowed whole with water, with or without food.

APPROVED INDICATIONS

NICE TA377: Pre Chemo
Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.

NICE TA316: Post Chemo
Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy.

ANTI-EMETICS AND SUPPORTIVE MEDICINES
Anti-emetics are not routinely required

INVESTIGATIONS / MONITORING REQUIRED
- FBC – Monthly initially, increasing up to every 3 months
- LFTs & U&Es – Monthly initially, increasing up to every 3 months
- PSA – 1 to 3 monthly, as indicated

ASSESSMENT OF RESPONSE
Clinical review 2 weeks after starting, then every 4 weeks. Treatment should continue until:
- Clinical Disease Progression OR
- Any 1 of the following (OR ≥ 2 of the following if clinical benefit):
  - PSA progression (>50% rise confirmed on 2 samples over baseline or nadir)
  - Bone scan new lesions (definite)
  - CT evidence of progression

REVIEW BY CLINICIAN
Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES
- Enzalutamide is a strong CYP3A4 enzyme inducer. Interactions with medicines which are eliminated via CYP3A4 metabolism are expected. This is one of the most important enzymes involved in the metabolism of drugs, so it is not possible to provide a complete list of medicines eliminated via this pathway, but examples include fentanyl, clarithromycin, cabazitaxel, warfarin, anti-epileptics, calcium channel blockers, dexamethasone, levothyroxine, simvastatin.

- Note that it may take up to one month for the full enzyme induction potential of enzalutamide to occur. Therefore, patients should be evaluated for loss of therapeutic effect of the CYP3A4 substrate during the first month of enzalutamide treatment.
- If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution
- Enzalutamide is also a moderate inducer of CYP2C9 (i.e. warfarin) and CYP2C19 (i.e. omeprazole) so may reduce the effectiveness of drugs metabolised by these routes.
- Co-administration with **warfarin** should be avoided
- CYP2C8 plays an important role in the metabolism of enzalutamide. The concomitant use of strong CYP2C8 inhibitors (gemfibrozil) or CYP2C8 inducers (only known drug is rifampicin) should be avoided if possible. If patients require a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80mg once daily. Note that trimethoprim is a moderate inhibitor and, as such, it is not necessary to reduce the enzalutamide dose.

MAIN TOXICITIES

- Hypertension
- Hot flush
- Headache
- Risk of seizures (occurred in 0.7% of trial patients)

DOSE MODIFICATIONS

Toxicities:

If a patient experiences ≥ Grade 3 toxicity or an intolerable adverse reaction, treatment should be withheld for one week or until symptoms improve to ≤ Grade 2. Then resume treatment at the same dose, or a reduced dose (120mg or 80mg) if warranted.

Hepatic Impairment

Note that a raised ALP in isolation is usually indicative of bone metastases, and in those circumstances, is not an indication for a dose reduction.
No dose reduction is required for patients with mild, moderate or severe (Child-Pugh A to C) however caution is required in severe hepatic impairment (Child-Pugh C) as an increased half-life of enzalutamide has been observed.

Renal Impairment

No dose reduction is required for patients with CrCl ≥ 30ml/min. There is no clinical data in patients with CrCl < 30ml/min and so caution is advised when treating this group

Hypertension

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 and temporary suspension of enzalutamide for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with enzalutamide may be resumed once hypertension is controlled

EXTRAVASATION

Not Applicable

TREATMENT LOCATION

Cancer Centre or Cancer Unit where there is an Oncologist with a specialisation in Urology

REFERENCES:

1. ENZALUTAMIDE (XTANDI®) - Summary of Product Characteristics. Date: December 2017. Available at https://www.medicines.org.uk/emc/product/3203 accessed 20/12/2017
2. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy Scher HI, et al. N Engl J Med. 2012; 367:1187-1197
3. National Institute for Health and Clinical Excellence 2014. Enzalutamide for metastatic hormone relapsed prostate cancer previously treated with a docetaxel containing regimen. TA316.
4. National Institute for Health and Clinical Excellence 2016. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. TA377.

Document Control

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Summary of Changes	1.1	Document approved.	
	1.2	Added reference to NHS England Circular re sequential us, updated CDF approval	
	1.3	Updated NICE approval	