Systemic Anti Cancer Treatment Protocol

Enzalutamide

PROCTOCOL REF: MPHAENZAL
(Version No: 1.0)

Approved for use in:

- The 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
- The treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Dosage:

Drug	Dosage	Route	Frequency
Enzalutamide	160mg	Oral	Daily

Continuous until disease progression or unacceptable toxicity

Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold

Supportive treatments:
No routine supportive treatments recommended

Extravasation risk:

Not applicable

Administration:

The capsules should be swallowed whole with water, and can be taken with or without food

Drug Interactions

Potential for other medicinal products to affect Enzalutamide exposures	*CYP2C8 inhibitors and inducers* Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily *CYP3A4 inhibitors and inducers* No dose adjustment is necessary when enzalutamide co-administered with inhibitors or inducers of CYP3A4.
Potential to affect exposures to other medicinal products	Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters. 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. The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment: Groups of medicinal products that can be affected include, but are not limited to: • Analgesics (fentanyl, tramadol) • Antibiotics (clarithromycin, doxycycline) • Anticoagulants (warfarin) • Antiepileptics (carbamazepine, clonazepam, phenytoin, primidone, valproic acid) • Antipsychotics (haloperidol) • Betablockers (bisoprolol, propanolol) • Calcium channel blockers (diltiazem, felodipine, nicardipine, nifedipine, verapamil) • Cardiac glycosides (digoxin) • Corticosteroids (dexamethasone, prednisolone) • HIV antivirals (indinavir, ritonavir) • Hypnotics (diazepam, midazolam, zolpidem) • Statins metabolized by CYP3A4 (simvastatin)

	• Thyroid agents (levothyroxine)

Patient counselling points

The capsules should be swallowed whole with water, and can be taken with or without food

Main Toxicities:

Enzalutamide	
Haematological toxicity	Neutropenia, leucopenia
Cardiovascular	Hot flush, hypertension
Nervous system disorders	Seizure, the mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to enzalutamide and its active metabolite binding to and inhibiting the activity of the GABA-gated chloride channel. Headache, cognitive disorder, memory impairment amnesia, disturbance in attention, visual hallucinations, anxiety
Skin and subcutaneous tissue disorders	Dry skin, pruritus
Musculoskeletal disorders	Fractures, myalgia, muscle spasms, muscular weakness, back pain

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	Ongoing
Medical Assessment	X	X	X		X	Every 12 weeks
Nursing Assessment		X	X	X	X	Every cycle
FBC	X		X	X	X	Every cycle
U&E & LFTs	X		X	X	X	Every Cycle

PSA	X	X	X	X	X	Every 4 weeks
CT scan	X					Every 12 weeks as clinically indicated
Informed Consent	X					
Blood pressure measurement	X	X	X	X	X	
PS recorded	X	X	X	X	X	
Toxicities documented	X	X	X	X	X	
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed on day 1 if:

WCC ≥ 3.0 x 10^9/L	ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Haematological toxicity is uncommon. If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L, discuss with the consultant before continuing treatment

Non-haematological toxicity:

Blood Pressure Guidance:
Pre-existing hypertension should be controlled (usually via the GP) before treatment with enzalutamide starts. Baseline blood pressure should be < 150/100mmHg.

Blood pressure management after Enzalutamide initiated	
Diastolic increase > 20mmHg above baseline or blood pressure rises to > 150/100mmHg	Antihypertensive therapy* may be required (or adjusted, if already on antihypertensives). Enzalutamide may continue
Blood pressure > 180/110mmHg	Enzalutamide therapy should be withheld until blood pressure controlled*

*** Manage hypertension according to current NICE guidelines:**

- For previously untreated patients > 55 years, use a calcium channel blocker first-line.

- Monitoring of BP and management until stabilised, may require GP involvement.

Hepatic impairment	
Enzalutamide is primarily hepatically eliminated, and is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). Caution is required in patients with moderate hepatic impairment (Child-Pugh Class B) as data in moderate hepatic impairment are not fully conclusive.	
Grade 1 AST or ALT increase to 2.5 times the upper limit of normal (ULN) Bilirubin increase to 1.5 times ULN	Repeat LFTs at two-weekly intervals. No dose reduction is required.
Grade 2 AST or ALT increase to 2.5 to 5 times ULN Bilirubin increase to 1.5 to 3 times ULN	Repeat LFTs one a week No dose reduction is required
Grade 3 AST or ALT over 5 times the ULN Bilirubin over 3 times the ULN	Withhold treatment immediately, along with any other potentially hepatotoxic medications. Repeat LFTs weekly until return to baseline or grade 1. Retreatment can be considered.
Grade 4 AST or ALT 20 times the ULN Bilirubin to 10 times the ULN	Treatment should be discontinued and patients should not be re-treated.

Renal impairment
Following oral administration of enzalutamide 70% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and approximately 15% is recovered in faeces No dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

For other grade 2 toxicities, including fatigue – consider dose reduction to 120mg daily.

References:

Xtandi 40mg capsules Enzalutamide. Summary of Product Characteristics, Astellas pharma l, 21/06/2013. Available from www.medicines.org.uk/emc/medicine. Last Updated 25/09/2014.

NICE TA 377