Systemic Anti Cancer Treatment Protocol

Enzalutamide

PROCTOCOL REF: MPHAENZAL
(Version No: 1.2)

The protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

The approved indication has also been temporarily expanded - please see the SRG Guidelines during COVID-19 Urology Cancer for further details.

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 during or after docetaxel therapy.

Dosage:

Drug	Dosage	Route	Frequency
Enzalutamide	160mg	Oral	Daily

- Continuous until disease progression or unacceptable toxicity.
- Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

* Caution should be used in administration 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 tablets 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. • The concomitant use of strong CYP3A4 inducers with enzalutamide is not recommended.
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) Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9 additional International Normalised Ratio (INR) monitoring should be conducted.

Please refer to the SPC for the full list of drug interactions

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

Please refer to the SPC or the full list of toxicities

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	Ongoing
Informed Consent	X					
Clinical Assessment	X	X	X	X		First three cycles and then every 12 weeks
SACT Assessment (to include PS and toxicities)	X	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 cycle
CT scan	X					If clinically indicated
Serum creatinine	X		X	X	X	Every cycle
Blood pressure measurement	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Enzalutamide is not myelosuppressive but FBC should be reviewed prior to each cycle.

If neutrophils < 1.0 x 10^9/L and/or platelets < 100x 10^9/L, continue drug therapy but **discuss with the clinical team prior to the next cycle.** If neutrophils < 0.5 x 10^9/L and/or platelets < 50x 10^9/L, **discuss with the clinical team 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 measurements	
Systolic 140-150 mmHg or Diastolic <90 mmHg:	Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary
Systolic 150-160mmHg or Diastolic 90-100mmgh:	-Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg.
Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):	Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg
Severe hypertension (>180mmHg systolic or >110mmHg diastolic)	Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once

	hypertension is appropriately controlled.

NICE Clinical Guideline CG 127- Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE

- 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	
No dose adjustment is necessary for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively). An increased half-life of enzalutamide has however been observed in patients with severe hepatic impairment. Enzalutamide 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	Treatment should be discontinued and patients should not be re-treated.

Bilirubin to 10 times the ULN	

Renal impairment
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 https://www.uptodate.com/contents/enzalutamide-drug-information?search=enzalutamide&topicRef=6942&source=see_link#F15036243

Xanti product monograph https://www.astellas.com