ENZALUTAMIDE

An option for men with hormone-refractory metastatic prostate cancer:

a) whose disease has progressed on or after docetaxel (NICE 2014)

or

b) for men who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated (NICE approved Jan 2016)

For both indications, no previous treatment with abiraterone, unless abiraterone has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression

Individual consent is not necessary for this drug

Drug / Dosage:	Enzalutamide	160mg	PO once daily throughout treatment
Administration:	Enzalutamide is available as 40mg capsules, which should be swallowed whole with water, with or without food.		
Frequency:	continuous treatment until disease progression or unacceptable toxicity		
Main Toxicities:	hot flush;	headache;	risk of seizures (occurred in 0.8% of trial patients)
Anti-emetics:	no anti-emetic routinely required		
Regular Investigations:	FBC		monthly initially, increasing up to every 3 months
	LFTs & U&Es		monthly initially, increasing up to every 3 months
	PSA		1 – 3 monthly, as indicated

Interactions:

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, rivaroxaban, apixaban, 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.

Also, when stopping enzalutamide, note that the half-life of enzalutamide is 5.8 days, and so 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.

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.

Co-administration with warfarin should be carried out with caution; with extra monitoring of INR during the first month of enzalutamide treatment, and warfarin dose adjustment made as appropriate.

Reason for Update: warfarin statement amended	Approved by Consultant: Dr R Laing
Version: 4	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 3	Date: 28.6.17
Prepared by: S Taylor	Checked by: C Tucker

Close monitoring of INR, with warfarin dose adjustment as necessary, is also required in the first few weeks following discontinuation of enzalutamide.
CYP2C8 plays an important role in the metabolism of enzalutamide. The concomitant use of strong CYP2C8 inhibitors (gemfibrozil) should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily.
Note that trimethoprim is a moderate inhibitor and, as such, it is not necessary to reduce the enzalutamide dose.[1]

Dose Modifications

Toxicities: If a patient experiences a ≥ 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 (120 mg or 80 mg) 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 adjustment is required for patients with mild hepatic impairment. Caution is required in patients with moderate hepatic impairment (Child-Pugh B).
Enzalutamide is not recommended in patients with severe hepatic impairment (Child-Pugh C).

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.

References: Cabot, R et al; NEJM 2012; 367: 1187 – 1197
Beer, T et al; NEJM 2014; 371: 424 - 433
[1]Letter on file from Astellas Pharma Ltd