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ARTICLE

Table 2 **Comparison of online drug interaction resources for enzalutamide***

Enzalutamide with / Resource	Oxycodone (metabolised by CYP3A4 (major), CYP2D6 (minor))	Mirtazapine (metabolised by CYP3A4)	Rivaroxaban (metabolised by CYP3A4, substrate of P-glycoprotein)	Apixaban (metabolised by CYP3A4, substrate of P-glycoprotein)	Dabigatran (substrate of P-glycoprotein)	Comments
Enzalutamide product information (Revised 2019 Sep 4)	No direct recommendation. In interaction section – 'analgesics' listed but not specifically oxycodone	No direct recommendation	No direct recommendation. In interaction section – anticoagulants, only warfarin listed	No direct recommendation. In interaction section – anticoagulants, only warfarin listed	Use with caution as dabigatran is a P-glycoprotein substrate and a drug with narrow therapeutic window	Difficult to quickly determine drug–drug interactions if you do not know how the other drug is metabolised
Australian Medicines Handbook (AMH)	Although no interaction found, need to consider pharmacokinetic and background information provided, which suggests ↓oxycodone. Consider an alternative or monitor pain relief and adjust oxycodone dose	Although no interaction found, need to consider pharmacokinetic and background information provided, which suggests ↓mirtazapine. Possible additive seizure risk	Although no interaction found, need to consider pharmacokinetic and background information provided and extrapolate from other potent CYP3A4 inducers. ↓rivaroxaban	Although no interaction found, need to consider pharmacokinetic and background information provided. However AMH does not suggest enzalutamide has any effect on P-glycoprotein, *so would assume no interaction*	Although no interaction found, need to consider pharmacokinetic and background information provided. However AMH does not suggest enzalutamide has any effect on P-glycoprotein, so *would assume no interaction*	Enzalutamide is not listed in specific P-glycoprotein substrate/inhibitor/inducer table which makes interaction interpretation difficult
MIMS Interaction Database	No interaction listed	No interaction listed	No interaction listed	No interaction listed	No interaction listed	Personal communication with MIMS editorial team (August 2019) that this content is under review
Stockley's Drug Interactions	Theoretical evidence predicts ↓oxycodone	Theoretical evidence predicts ↓mirtazapine	Theoretical evidence predicts ↓rivaroxaban, but confusing as no information to suggest enzalutamide's effect on P-glycoprotein#	Theoretical evidence predicts ↓apixaban, but confusing as no information to suggest enzalutamide's effect on P-glycoprotein#	Use with caution as may increase dabigatran	Enzalutamide not listed in specific P-glycoprotein substrate/inhibitor/inducer table, although role of P-glycoprotein is mentioned in dabigatran/enzalutamide interaction
Lexicomp Drug Interactions	Risk Rating D: need to consider dose modification as ↓oxycodone	Risk Rating D: need to consider dose modification as ↓mirtazapine	Risk Rating X: avoid – see comments	Risk Rating X: avoid	No interactions identified	For rivaroxaban, there is a statement that in Canada these combinations would say 'use with caution' rather than 'avoid'
Micromedex Drug Interactions	Major interaction. ↓oxycodone	No interaction listed	No interaction listed	No interaction listed	No interaction listed	Micromedex, a US database, less commonly referred to for drug–drug interaction advice
Cancer Drug Interactions	Do not co-administer# If co-administration clinically necessary, close monitoring required	Do not co-administer# If co-administration clinically necessary, may need to increase mirtazapine dose as enzalutamide ↓mirtazapine	Do not co-administer# If co-administration clinically necessary, close monitoring of anti-Xa recommended	Do not co-administer# If co-administration clinically necessary, close monitoring for anti-Xa recommended	Potential Interaction# If co-administration clinically necessary, close monitoring for dabigatran toxicity recommended	

* Resources in this table reviewed online 2019 Aug 23.

Notes

Enzalutamide, an anti-androgen for metastatic castration-resistant prostate cancer, will be increasingly seen in the community. It is an unrecognised, yet major contributor to drug interactions and has a particularly complex metabolism.

It is a potent CYP3A4 inducer, moderate CYP2C9 and CYP2C19 inducer, but its effect on P-glycoprotein is conflicting in the manufacturer's information. This, combined with the limited published reports of clinical outcomes from drug interactions to date, has resulted in variation or, in some cases, an absence of reporting of drug–drug interactions. In addition, the extended half-life (approximate mean 6 days) makes drug–drug interactions difficult to predict, with maximum induction potential occurring up to one month from starting enzalutamide, and effects on enzymes continuing for at least one month after cessation. Management of anticoagulation in patients taking enzalutamide is particularly challenging and input from a haematologist is recommended.

Enzalutamide has complex metabolism:

- substrate CYP2C8 (major), CYP3A4 (minor)
- induces CYP3A4 (potent), CYP2C9 and CYP2C19 (moderate)
- product information says in vitro enzalutamide inhibits P-glycoprotein but it also says it may act as an inducer
- induces CYP2B6, OAT, UGT

Resource comments that these combinations have not actually been clinically studied

CYP cytochrome P450

↓ reduces drug concentration

An A3 single-page version of this table is available online.

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