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REVIEW ARTICLE

Enzalutamide: Understanding and Managing Drug Interactions to Improve Patient Safety and Drug Efficacy

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Abstract

Enzalutamide is an oral androgen receptor signaling inhibitor utilized in the treatment of men with prostate cancer. It is a moderate inducer of the cytochrome P450 (CYP) enzymes CYP2C9 and CYP2C19, and a strong inducer of CYP3A4. It was also shown to be a mild inhibitor of the efflux transporter P-glycoprotein in patients with prostate cancer. Enzalutamide is primarily metabolized by CYP3A4 and CYP2C8. The risk of enzalutamide drug interactions arises primarily when it is coadministered with other drugs that interact with these CYPs, including CYP3A4. In this review, we begin by providing an overview of enzalutamide including its dosing, use in special populations, pharmacokinetics, changes to its prescribing information, and potential for interaction with coadministered drugs. Enzalutamide interactions with drugs from a wide range of medication classes commonly prescribed to patients with prostate cancer are described, including oral androgen deprivation therapy, agents used to treat a range of cardiovascular diseases, antidiabetic drugs, antidepressants, anti-seizure medications, common urology medications, analgesics, proton pump inhibitors, immunosuppressants, and antigout drugs. Enzalutamide interactions with common vitamins and supplements are also briefly discussed. This review provides a resource for healthcare practitioners and patients that will help provide a basis for the understanding and management of enzalutamide drug–drug interactions to inform decision making, improve patient safety, and optimize drug efficacy.

Plain Language Summary

Enzalutamide is a drug that is used to treat various stages of advanced prostate cancer, a type of cancer that begins in the prostate and may spread beyond the prostate. Enzalutamide stops testosterone from stimulating prostate cancer growth. Like other drugs, enzalutamide enters the bloodstream, and then is processed and removed from the body. Sometimes, when a person takes multiple drugs, one drug can make it difficult for the body to process and remove one or more of the other drugs. This is referred to as a drug interaction. Enzalutamide drug interactions can cause the level of other drugs in the body to increase or decrease in an abnormal way. It is also possible for certain other drugs to alter the levels of enzalutamide. Drug interactions that cause the level of a drug to get too low can prevent that drug from working effectively, whereas drug interactions that cause the level of a drug to get too high can lead to side effects of that drug. People with prostate cancer are mostly aged 65 years or older and often take medications to treat a variety of diseases. Examples include medications to treat heart conditions, diabetes, high cholesterol, high blood pressure, and many other conditions. Here, we describe enzalutamide drug interactions with these types of medications. Our goal is to provide a resource to help healthcare providers and patients better understand enzalutamide drug interactions and how to manage them to improve patient safety and drug effectiveness.

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Key Points

Enzalutamide is a beneficial drug for the treatment of certain types of prostate cancer but requires management of potentially significant drug interactions.

Most drug interactions stem from the fact that enzalutamide is a strong inducer of CYP3A4, a hepatic cytochrome P450 enzyme that is responsible for the metabolism of many other drugs on the market.

Based on the current understanding of enzalutamide drug interactions, nearly all of them can be effectively managed with appropriate knowledge of which drugs pose interaction risks, when dose adjustments are indicated, and when alternative drugs can be substituted.

1 Introduction

After lung cancer, prostate cancer was the second most diagnosed cancer in men in 2020 with an estimated 1.4 million new cases and 375,000 deaths worldwide [1]. The estimated number of new prostate cancer cases in the USA in 2023 is approximately 300,000 with 35,000 deaths [2]. Age is a risk factor for the onset of prostate cancer [3], and the median age at diagnosis is 67 years [2]. Men over 65 years of age commonly have other age-related comorbidities in addition to prostate cancer and the likelihood that prostate cancer will be associated with more comorbidities increases with increasing age at diagnosis [4].

Because older patients frequently have multiple health conditions, they are often prescribed many drugs in what is referred to as "polypharmacy" [5]. The presence of many coadministered medications puts patients at heightened risk for drug–drug interactions (DDIs) [5]. Therefore, it is critical to check for potential DDIs when prostate cancer drugs are given with other agents used to treat comorbidities. The goal of this review is to provide a resource to healthcare providers to improve their understanding of DDIs for the prostate cancer drug enzalutamide and enable them to make informed treatment decisions. Clinically, this is important as DDIs between enzalutamide and certain other medicines may result in a loss of efficacy of the coadministered drug or an increased risk of drug-related adverse effects [6–8].

In this review, we first provide a brief background describing types of DDIs and the roles of cytochrome P450 (CYP) enzymes and drug transporters in regulating plasma drug concentrations. We then describe enzalutamide, including its dosing, use in special populations, pharmacokinetics, changes to its prescribing information, and the basis for its potential interactions with coadministered drugs. Finally, the focus of the review is on describing DDIs between enzalutamide and other drugs commonly prescribed to patients with prostate cancer. Where data are available, we also briefly describe potential interactions between enzalutamide and commonly used vitamins and herbal supplements.

We did not use a strict *a priori* method for the literature search in this review. Instead, we generated a list of drugs and drug classes to consider for enzalutamide DDIs based on the authors' input and clinical expertise. This list was based on the most common drugs utilized by the population of patients who are receiving prostate cancer therapy, i.e., those who are male, elderly, and with common comorbidities including heart disease and diabetes. Descriptions of individual DDIs, including a more detailed description of specific cases, relied on information obtained from multiple sources including drug prescribing information, Drugs.com [9], UpToDate (Lexicomp) [10], the Prescriber's Digital Reference [11], literature sources identified via PubMed and Google Scholar searches using the drug names and classes in Table 1 as search terms, and the individual and collective expertise of the authors.

2 Molecular and Physiologic Basis for Drug–Drug Interactions (DDIs)

2.1 Types of DDIs

DDIs include pharmacokinetic and pharmacodynamic interactions [12] (Table 2). Pharmacokinetic interactions primarily consist of metabolic interactions involving CYP enzymes and include drug–transporter interactions, plasma protein DDIs, and absorptive DDIs [12]. Pharmacodynamic interactions typically consist of additive effects of two associated drugs [12]. DDIs may also impact the metabolic conversion of prodrugs, which are inactive drug precursors, to their active metabolites [13, 14].

2.2 Cytochrome P450 (CYP) Enzymes

Human CYP enzymes are the major enzymes responsible for drug metabolism and account for ~75% of drugs processed by enzymes [15]. CYP enzymes increase the hydrophilicity of compounds to aid in their excretion from the body and CYP-mediated drug metabolism plays a critical role in determining treatment outcomes by influencing drug action, safety, bioavailability, and resistance [15]. CYPs also convert certain prodrugs to their active metabolites [15]. The activity and expression levels of individual CYPs can vary significantly among individuals because of genetic

Table 1 Potential drug interactions with enzalutamide and recommendations for management

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
ADT (subcutaneous injection)	Leuprolide	Advanced prostate cancer	None	None	None	No concerns
ADT (subcutaneous injection)	Goserelin	Advanced prostate cancer	None	None	None	No concerns
ADT (intramuscular injection)	Triptorelin	Advanced prostate cancer	None	None	None	No concerns
ADT (subcutaneous injection)	Degarelix	Advanced prostate cancer	None	None	None	No concerns
ADT (oral)	Relugolix	Advanced prostate cancer	CYP3A4, CYP2C8, and P-gp substrate; CYP3A and CYP2B6 inducer	Decrease/no effect	None	No concerns
Anticoagulants	Apixaban	DVT; PE; stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation, DVT prophylaxis, and PE prophylaxis	CYP3A4, P-gp, and BCRP substrate	Unclear because of opposing effects on CYP3A4 and P-gp	None	Strong CYP3A4 inducers such as enzalutamide may decrease the serum concentration of apixaban. Dose adjustment may not be required but therapy modification should be considered
	Rivaroxaban	Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation; treatment of VTE, such as DVT and PE, including after knee, hip, or cardiac surgery	CYP3A4/5 and P-gp substrate	Unclear because of opposing effects on CYP3A4 and P-gp	None	Strong CYP3A4 inducers such as enzalutamide may decrease the serum concentration of rivaroxaban. Dose adjustment may not be required but therapy modification should be considered
	Dabigatran	Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation; VTE, including DVT, PE, cerebral thromboembolism (e.g., cerebral venous sinus thrombosis), and central line thrombosis; thrombosis prophylaxis including DVT prophylaxis and PE prophylaxis	P-gp substrate	Increase	None	Monitor therapy. Reduce dabigatran dose or avoid coadministration in renally impaired patients
	Edoxaban	Stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation; treatment of DVT or PE after 5–10 days of initial therapy with a parenteral anticoagulant	P-gp substrate	Increase	None	Dose adjustment may not be required but therapy modification should be considered
	Warfarin	Treatment of DVT or PE and for DVT prophylaxis or PE prophylaxis; thrombosis prophylaxis (i.e., arterial thromboembolism prophylaxis, stroke prophylaxis, or coronary artery thrombosis prophylaxis)	CYP2C9 and CYP3A4 substrate	Decrease	None	Consider modifying therapy
Antiplatelet agents	Clopidogrel	Arterial thromboembolism prophylaxis (i.e., MI prophylaxis, stroke prophylaxis, thrombosis prophylaxis), including in persons with acute MI, STEMI, NSTEMI, or unstable angina	Substrate and inhibitor of CYP2C19 and strong CYP2C8 inhibitor	Increase	Increase	Monitor therapy
	Ticagrelor	Arterial thromboembolism prophylaxis in patients with ACS (unstable angina, acute MI), including those undergoing PCI; reduction in risk of first MI (MI prophylaxis) or stroke in patients with CAD at high risk for these events; stroke prophylaxis in patients with acute ischemic stroke or high-risk TIA	CYP3A4 substrate	Decrease	None	Avoid coadministration

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Prasugrel	Arterial thromboembolism prophylaxis (including stent thrombosis) in persons with acute coronary syndrome (i.e., unstable angina, acute MI, NSTEMI, or STEMI) who are to be managed with PCI	CYP3A4, CYP2C9, and CYP2C19 substrate PK not affected by CYP3A4 inducers	None	None	No concerns
	Aspirin	Secondary stroke prophylaxis in patients who have had an ischemic stroke or TIA	None	None	None	No concerns
Statins	Atorvastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control; for the purpose of reducing the risk of CV events (e.g., MI prophylaxis, stroke prophylaxis)	CYP3A4 and P-gp substrate, P-gp inhibitor	Decrease	None	Monitor therapy
	Simvastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control; for the purpose of reducing the risk of CV events (e.g., MI prophylaxis, stroke prophylaxis)	CYP3A4 substrate	Decrease	None	No concerns
	Lovastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control	CYP3A4 substrate	Decrease	None	No concerns
	Fluvastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control; for the purpose of reducing the risk of CV events (e.g., MI prophylaxis, stroke prophylaxis)	CYP2C9, CYP2C8, and CYP3A4 substrate	Decrease	None	Monitor therapy
	Pitavastatin	Adjunctive therapy to diet in adult patients with primary hyperlipidemia or mixed dyslipidemia to reduce elevated total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, and to increase HDL cholesterol	Minor CYP2C9 substrate	None	None	No concerns
	Pravastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control; MI prophylaxis or stroke prophylaxis	None	None	None	No concerns
	Rosuvastatin	Treatment of hypercholesterolemia, including hyperlipidemia, hyperlipoproteinemia, or hypertriglyceridemia, as an adjunct to dietary control; primary prevention of CV disease (including MI prophylaxis and stroke prophylaxis) and to reduce the risk of arterial revascularization procedures in patients without evidence of coronary heart disease but who have risk factors for CV disease	BCRP substrate	No change	None	No concerns

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
Ca channel blockers	Amlodipine	Treatment of hypertension	CYP3A4 substrate	Decrease	None	Monitor therapy
	Diltiazem	Hypertension; chronic stable angina; variant angina; atrial flutter, atrial fibrillation, or paroxysmal supraventricular tachycardia; ongoing ischemia in acute MI, STEMI, NSTEMI, or unstable angina; idiopathic dilated cardiomyopathy	CYP3A4 substrate and inhibitor	Decrease	None	Consider modifying therapy
	Verapamil	Variant angina and chronic stable angina; rapid conversion of narrow-complex paroxysmal supraventricular tachycardia to sinus rhythm; paroxysmal supraventricular tachycardia prophylaxis due to re-entry; atrial flutter or atrial fibrillation; hypertension	CYP3A4 and P-gp substrate and inhibitor	Decrease	None	Consider modifying therapy
ACE inhibitors	Benazepril	Hypertension	None	None	None	No concerns
	Lisinopril	Hypertension, heart failure, acute MI for reduction in cardiovascular mortality	None	None	None	No concerns
	Captopril	Hypertension, heart failure, left ventricular dysfunction post-MI, hypertensive urgency, or hypertensive emergency	P-gp inhibitor	None	None	No concerns
Beta-blockers	Carvedilol	Treatment of essential hypertension, either as a single agent or in combination with other antihypertensive agents	CYP2C9, CYP3A4, CYP2C19, and P-gp substrate	Decrease	None	No concerns
	Metoprolol succinate	Treatment hypertension, angina, heart failure, acute MI, and heart rate control in patients with atrial fibrillation or atrial flutter	CYP2D6 substrate	None	None	No concerns
	Bisoprolol fumarate	Treatment of hypertension, heart failure, angina, and heart rate control in patients who have atrial fibrillation or atrial flutter	None	None	None	No concerns
Antiarrhythmic agents	Disopyramide	Documented, life-threatening arrhythmias such as sustained ventricular tachycardia	CYP3A4 substrate	Decrease	None	Monitor therapy. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Quinidine	Conversion to and/or maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or ventricular tachycardia; treatment of supraventricular tachycardia; paroxysmal supraventricular tachycardia prophylaxis in patients with re-entrant tachycardia, including patients with Wolff–Parkinson–White syndrome	CYP3A4 and P-gp substrate; P-gp inhibitor	Decrease	None	Monitor therapy. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Procainamide	Ventricular tachycardia with pulses (stable monomorphic or wide-complex regular ventricular tachycardia) during CPR in patients with preserved left ventricular function	None	None	None	Avoid coadministration if the patient has a prolonged QTc Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Amiodarone	Life-threatening recurrent ventricular fibrillation or hemodynamically unstable (symptomatic) sustained ventricular tachycardia, including post-MI patients	CYP3A4 and CYP2C8 substrate; CYP3A4, 2C9, 2D6, and 1A2 inhibitor	Decrease	None	Monitor therapy. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Dofetilide	Conversion of atrial fibrillation/atrial flutter to normal sinus rhythm; or for maintenance therapy of patients with highly symptomatic atrial fibrillation/atrial flutter of 1 week or more duration	CYP3A4 substrate	Decrease	None	Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Sotalol	Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or atrial flutter who are currently in sinus rhythm	None	None	None	Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Flecainide	Prevention of life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia (i.e., ventricular tachycardia prophylaxis)	None (CYP2D6 substrate)	None	None	Avoid coadministration if the patient has a prolonged QTc Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Propafenone	Life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia	CYP2D6 and CYP3A4 substrate; P-gp inhibitor	Unclear because of opposing effects on CYP3A4 and P-gp	None	Monitor for decreased propafenone effects or therapeutic failure. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Digoxin	Heart failure and atrial fibrillation	P-gp substrate	Increase	None	No concerns
Angiotensin II receptor blocker	Valsartan	Hypertension; heart failure	CYP2C9 substrate	None	None	No concerns
	Losartan	Hypertension and stroke prophylaxis in hypertensive patients with left ventricular hypertrophy	Primarily metabolized by CYP2C9 and to a lesser extent CYP3A4	Decrease	None	Monitor therapy
	Olmesartan	Hypertension	None	None	None	No concerns
Angiotensin receptor/neprilysin inhibitor	Sacubitril/valsartan	Heart failure, including for reduction in CV mortality and reduction in heart failure hospitalizations	Valsartan is a CYP2C9 substrate	None	None	No concerns
Mineralocorticoid receptor antagonists	Spironolactone	Hypertension	CYP3A4/5 substrate, CYP3A4/5 inhibitor	Decrease	None	No concerns
	Eplerenone	Treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents	CYP3A4 substrate	Decrease	None	Monitor therapy
Sulfonylureas	Glyburide	Treatment of T2DM as an adjunct to diet and exercise	CYP2C9 and P-gp substrate	Unclear because of opposing effects on CYP2C9 and P-gp	None	Monitor therapy
	Glimepiride	Treatment of T2DM as an adjunct to diet and exercise	CYP2C9 substrate	Decrease	None	Monitor therapy
DPP4 inhibitors	Saxagliptin	Treatment of T2DM as an adjunct to diet and exercise	CYP3A4/5 and P-gp substrate	Unclear because of opposing effects on CYP3A4/5 and P-gp	None	Monitor therapy
Biguanide	Metformin	Treatment of T2DM as an adjunct to diet and exercise	None	None	None	No concerns
SGLT2 inhibitors	Canagliflozin	Treatment of T2DM as an adjunct to diet and exercise; to reduce cardiovascular mortality and MACE in patients with T2DM with established cardiac disease; to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and reduction in heart failure hospitalizations and CV death in adults with T2DM and diabetic nephropathy with albuminuria more than 300 mg/day	P-gp substrate	None	None	No concerns

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Dapagliflozin	Treatment of T2DM as an adjunct to diet and exercise; reduction in heart failure hospitalizations in adults with T2DM and established CV disease or multiple CV risk factors; treatment of reduced ejection fraction heart failure and preserved ejection fraction heart failure for reduction in CV mortality and hospitalization for heart failure; treatment of chronic kidney disease to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in those at risk of disease progression	None	None	None	No concerns
	Empagliflozin	Treatment of T2DM as an adjunct to diet and exercise; reduction in cardiovascular MACE in patients with T2DM with established CV disease; reduction in CV death and reduction in heart failure hospitalizations in adults with heart failure	None	Increase	None	No concerns
SSRIs	Citalopram	Major depression	Mild CYP2C19 inhibitor	None	None	Monitor therapy. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Fluoxetine	Major depression	CYP2D6 substrate CYP2D6 and CYP2C19 inhibitor; weak inhibitor of CYP3A4 and CYP2C9	None	None	Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Sertraline	Major depression	CYP2D6 inhibitor	None	None	Monitor therapy. Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
SNRIs	Venlafaxine	Major depression	CYP2D6 inhibitor	None	None	Avoid coadministration if the patient has a prolonged QTc. Otherwise, potential risks of DDIs with enzalutamide and drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully managed
	Desvenlafaxine	Major depression	CYP2D6 inhibitor	None	None	No concerns
	Duloxetine	Major depression	CYP2D6 substrate and inhibitor	None	None	No concerns
Antiseizure medications	Carbamazepine	Management of generalized tonic-clonic seizures or for partial seizures, either simple or complex partial seizures	CYP3A4 substrate, potent CYP3A4 inducer	Decrease	Decrease	Consider modifying therapy
	Phenobarbital	Treatment of status epilepticus; maintenance treatment of all types of seizures, including but not limited to partial, myoclonic, tonic-clonic, or neonatal seizures not responding to other anticonvulsants	CYP2C9 substrate; CYP3A and P-gp inducer	Decrease	Decrease	Consider modifying therapy
	Phenytoin	Status epilepticus; treatment of tonic-clonic seizures or partial seizures	CYP2C9 substrate; CYP3A4, CYP2C9, CYP2C19 inducer	Decrease	Decrease	Consider modifying therapy
	Primidone	Alternative to other anticonvulsants for the management of generalized tonic-clonic seizures, or for the management of complex partial seizures (e.g., psychomotor seizures)	CYP2C9 substrate; CYP3A4 and P-gp inducer	Decrease	Decrease	Consider modifying therapy
	Valproic acid	Monotherapy or adjunct treatment of absence seizures (simple and complex) or complex partial seizures, and adjunctively for other seizure types that include absence or complex partial seizures (e.g., tonic-clonic seizures, myoclonic seizures)	CYP2C9 substrate (minor)	None	None	No concerns
	Lamotrigine	Treatment of partial seizures with or without secondary generalization; adjunctive therapy to other anticonvulsants in the treatment of primary generalized tonic-clonic seizures; adjunctive therapy to other anticonvulsants in the treatment of generalized seizures of Lennox–Gastaut syndrome	None	None	None	No concerns
	Gabapentin	Adjunctive treatment of partial seizures with or without secondary generalized tonic-clonic seizures	None	None	None	No concerns
	Topiramate	Treatment of partial seizures (monotherapy or adjunctive therapy)	CYP3A4 (weak inducer), CYP2C19 (weak inhibitor)	None	None	No concerns
Common urology medicines	Oxybutynin	Treatment of OAB or neurogenic bladder with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency	CYP3A4 substrate	Decrease	None	No concerns
	Mirabegron	Treatment of OAB or neurogenic bladder with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency	P-gp substrate	Increase	None	Monitor therapy

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Trospium	Treatment of OAB with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency, including neurogenic bladder	None	None	None	No concerns
	Tamsulosin	Treatment of the signs and symptoms of BPH	CYP3A4 substrate	Decrease	None	No concerns
Immunosuppressants	Cyclosporine	Kidney, heart, and liver transplant rejection prophylaxis; treatment of severe rheumatoid arthritis, severe plaque psoriasis, ocular inflammation associated with dry eye disease, and ulcerative colitis	CYP3A4 substrate and inhibitor; CYP2C8 inhibitor; P-gp substrate and inhibitor	Decrease	Increase	Monitor therapy
	Tacrolimus	Liver, kidney, lung, heart, pancreas, and islet transplant rejection prophylaxis; treatment of psoriasis, uveitis, dermatitis, and lupus nephritis	CYP3A4 substrate	Decrease	None	Monitor plasma concentrations of tacrolimus closely and adjust dosage accordingly
	Everolimus	Kidney and liver transplant rejection prophylaxis	CYP3A4 and P-gp substrate	Decrease	None	Concomitant use of strong CYP3A4 inducers and everolimus should be avoided if possible Monitor therapy closely Dose increases of everolimus may be necessary
	Sirolimus	Kidney and heart transplant rejection prophylaxis	CYP3A4 and P-gp substrate	Decrease	None	Concomitant use of strong CYP3A4 inducers and sirolimus should be avoided if possible Monitor therapy closely Dose increases of sirolimus may be necessary
Antigout drugs	Colchicine	Acute gout or gouty arthritis flare; gout prophylaxis	CYP3A4 and P-gp substrate	Decrease	None	Monitor therapy
	Naproxen sodium	Acute gout	CYP2C8 and CYP2C9 substrate	Decrease	None	Monitor therapy
	Prednisone	Acute gout or gouty arthritis as adjunctive therapy	CYP3A4 and P-gp substrate,	Decrease	None	Monitor therapy
	Allopurinol	Primary or secondary gout (i.e., acute attacks, tophi, gouty arthritis or joint destruction, uric acid lithiasis, and/or uric acid nephropathy)	None	None	None	No concerns
Opioid analgesics	Oxycodone	Treatment of severe pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	CYP3A4 substrate	Decrease	None	Monitor therapy Consider an oxycodone dose increase until stable drug effects are achieved If enzalutamide is discontinued, monitor for respiratory depression, and consider an oxycodone dose reduction until stable drug effects are achieved

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Methadone	For the treatment of opiate agonist dependence; treatment of moderate pain or severe pain	CYP3A4 and P-gp substrate	Decrease	None	Monitor therapy Monitor for withdrawal symptoms upon initiation of enzalutamide or increase in enzalutamide dose If enzalutamide is discontinued, monitor for adverse methadone effects, including sedation and respiratory depression
	Tramadol	Treatment of severe pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	CYP3A4 substrate	Decrease	None	Monitor therapy Monitor patients closely for decreased efficacy of tramadol when it is combined with enzalutamide and for signs of tramadol toxicity when enzalutamide is discontinued
	Fentanyl	Treatment of severe pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	CYP3A4 and P-gp substrate	Decrease	None	Monitor therapy Patients should be closely monitored for loss of analgesia and withdrawal symptoms when fentanyl is combined with enzalutamide and for potential fentanyl toxicity when enzalutamide is discontinued
	Morphine	Treatment of acute and chronic severe pain requiring an opioid analgesic and for which alternative treatments are inadequate	P-gp substrate	Increase	None	No concerns
	Hydromorphone	Treatment of severe pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate	None	None	None	No concerns
	Oxymorphone	Treatment of severe pain	None	None	None	No concerns
PPIs	Omeprazole	Short-term self-treatment of frequent dyspepsia or pyrosis (heartburn) that occurs ≥2 times per week; treatment of erosive esophagitis (erosive GERD); treatment of nonerosive GERD; short-term treatment of active benign gastric ulcer; short-term treatment of active duodenal ulcer; *Helicobacter pylori* eradication	CYP2C19 and CYP3A4 substrate, CYP2C19 inhibitor	Decrease	None	Monitor therapy
	Lansoprazole	Short-term treatment of frequent dyspepsia or pyrosis (heartburn) that occurs ≥2 times per week; treatment of non-erosive GERD; long-term treatment of pathological hypersecretory conditions, including Zollinger–Ellison syndrome; *H. pylori* eradication	CYP2C19 and CYP3A4 substrate	Decrease	None	No concerns
	Pantoprazole	Treatment of erosive esophagitis (erosive GERD); treatment of pathological hypersecretion associated with Zollinger–Ellison syndrome or other hypersecretory syndromes; short-term treatment of frequent dyspepsia or pyrosis (heartburn) that occurs ≥2 times per week; treatment of nonerosive GERD; healing of duodenal ulcer; healing of gastric ulcer; *H. pylori* eradication	CYP2C19 and CYP3A4 substrate	Decrease	None	No concerns

Table 1 (continued)

Drug class	Drugs	Indications[a]	Enzalutamide-relevant metabolism[a]	Potential enzalutamide effect on drug exposure[b]	Potential drug effect on enzalutamide exposure[b]	Management/notes[c]
	Esomeprazole	Treatment of symptomatic, nonerosive GERD; treatment of diagnostically confirmed erosive esophagitis due to GERD; short-term self-treatment of frequent dyspepsia or pyrosis (heartburn) that occurs ≥2 times per week; treatment of pathological hypersecretion associated with Zollinger–Ellison syndrome; *H. pylori* eradication	CYP2C19 and CYP3A4 substrate, CYP2C19 inhibitor	Decrease	None	No concerns
	Dexlansoprazole	Symptomatic treatment of nonerosive GERD, including treatment of pyrosis (heartburn) related to GERD; treatment of erosive esophagitis	CYP2C19 and CYP3A4 substrate	Decrease	None	No concerns
	Rabeprazole	Symptomatic treatment of nonerosive GERD; treatment of erosive esophagitis (erosive GERD); healing of duodenal ulcer; treatment of pathological hypersecretory conditions including Zollinger–Ellison syndrome; *H. pylori* eradication	CYP2C19 substrate	Decrease	None	No concerns

ACE angiotensin-converting enzyme, *ACS* acute coronary syndrome, *ADT* androgen deprivation therapy, *BCRP* breast cancer resistance protein, *BPH* benign prostatic hyperplasia, *Ca* calcium, *CAD* coronary artery disease, *CPR* cardiopulmonary resuscitation, *CV* cardiovascular, *CYP* cytochrome P450, *DDI* drug–drug interaction, *DPP* dipeptidyl peptidase, *DVT* deep vein thrombosis, *eGFR* estimated glomerular filtration rate, *EKG* electrocardiogram, *GERD* gastroesophageal reflux disease, *H. pylori Helicobacter pylori*, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MACE* major cardiovascular event, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *OAB* overactive bladder, *PE* pulmonary embolism, *PCI* percutaneous coronary intervention, *P-gp* P-glycoprotein, *PK* pharmacokinetics, *PPI* proton pump inhibitor, *QTc* QT interval corrected for heart rate, *SGLT2* sodium-glucose co-transporter 2, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* serotonin-selective reuptake inhibitor, *STEMI* ST-elevation myocardial infarction, *TIA* transient ischemic attack, *T2DM* type 2 diabetes mellitus, *VTE* venous thromboembolism

[a]Information in the "Indications" and "Enzalutamide-relevant metabolism" columns is from the prescribers' digital reference [11]. Included indications are those that are relevant to diseases/disorders discussed in the article

[b]Information in the "Predicted enzalutamide effect on drug exposure" and "Predicted drug effect on enzalutamide exposure" columns is inferred based on information in the "Enzalutamide-relevant metabolism" column

[c]The information in the "Management/notes" column is derived from the UpToDate Drug Interactions Tool (part of the Lexicomp database) [10], the Interaction Checker of Drugs.com [9], as well as author expertise (i.e., for managing potential DDIs associated with QTc prolongation). The UpToDate Drug Interactions Tool and the Drugs.com Interaction Checker allow users to search for medications and analyze potential DDIs

differences [16, 17] and this is important to keep in mind when monitoring DDIs, as patients may not respond to drugs in the predicted manner. CYPs are mainly expressed in the liver, but also in the kidney, placenta, adrenal gland, gastrointestinal tract, and skin [15]. Approximately 80% of clinical drugs are metabolized by members of the CYP1, CYP2, and CYP3 families [18, 19]. CYP enzyme induction results from an increase in the amount of CYP enzymes and/or CYP enzymatic activity. CYP induction may in turn result in altered drug metabolism, such that the drug effect may be either decreased or remain unchanged. Conversely, CYP enzyme inhibition results from a decrease in CYP enzymatic activity. CYP inhibition may result in decreased drug metabolism and potentially increased drug concentration.

2.3 Drug Transporters: P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP)

Membrane transporters play key roles in the pharmacokinetics, safety, and efficacy of drugs [20]. These include P-gp (also known as multidrug resistance 1 [MDR1]), BCRP (also known as ABCG2), organic cation transporters (OCTs), organic anion transporters (OATs), and organic anion transporting polypeptides (OATPs) [20]. P-gp and BCRP are major transporters that regulate absorption, disposition, and excretion of many drugs and play key roles in DDIs [20, 21]. P-gp is expressed in the small intestine, kidney, liver, and brain endothelium [20] where it plays a role in the blood–brain barrier (BBB) in limiting entry of various drugs into the central nervous system [20]. P-gp is also involved in intestinal absorption and intestinal, biliary, and urinary excretion of drugs [20]. BCRP is expressed in the gastrointestinal tract, liver, kidney, brain endothelium, mammary tissue, testes, and placenta [20]. BCRP limits oral bioavailability and the transport of some substrates across the BBB, blood–testes barrier, and maternal–fetal barrier [20]. P-gp/BCRP enzyme induction results from an increase in the amount of P-gp/BCRP enzymes and/or the enzymatic activity of P-gp/BCRP [21], and both transporters are transcriptionally regulated by the pregnane xenobiotic receptor (PXR) [21–23]. Drug-induced activation of PXR and subsequent induction of drug-metabolizing enzymes and transporters are central mechanisms driving DDIs [24]. Decreased drug absorption and decreased drug concentration following P-gp/BCRP induction can result in the drug effect being either decreased or remaining unchanged. Conversely, P-gp/BCRP enzyme inhibition resulting from a decrease in P-gp/BCRP transporter activity has the potential to cause DDIs.

3 Enzalutamide

Enzalutamide is a nonsteroidal androgen receptor signaling inhibitor indicated for the treatment of men with advanced metastatic hormone-sensitive prostate cancer (HSPC) and castration-resistant prostate cancer (CRPC) [25–28], as well as nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high risk of metastasis [29].

3.1 Dosing

Enzalutamide is administered once-daily via oral dosing (160 mg) [6, 30, 31]. Patients receiving enzalutamide for advanced prostate cancer (HSPC and CRPC) should be undergoing testosterone suppression, i.e., they should be receiving a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy [26].

3.2 Pharmacokinetics

The median time to peak drug concentration (T_{max}) of enzalutamide is 1 hour following a single 160 mg dose of capsules and 2 hours following a single 160 mg dose of tablets [32]. The mean volume of distribution is 110 L (29%) after a single oral dose [32]. Enzalutamide is 97–98% bound to plasma proteins, primarily albumin, and its active metabolite, *N*-desmethyl enzalutamide, is 95% bound to plasma proteins [6]. Enzalutamide is primarily metabolized by CYP3A4 and CYP2C8 to form the active metabolite *N*-desmethyl enzalutamide and an inactive carboxylic acid metabolite [33]. Clinical DDI studies evaluating the effect of a strong CYP2C8 and a strong CYP3A4 inhibitor on the combined pharmacokinetics of enzalutamide and *N*-desmethyl enzalutamide and the effect of enzalutamide on the pharmacokinetics of oral dose-sensitive substrates for CYP2C8, CYP2C9, CYP2C19, or CYP3A4 have indicated that enzalutamide is a moderate inducer of CYP2C9 and CYP2C19, and a strong inducer of CYP3A4 [33]. The mean terminal half-life ($t_{1/2}$) for enzalutamide after a single oral dose is 5.8 days (2.8–10.2 days); enzalutamide achieves steady state 28 days following administration [32]. The mean $t_{1/2}$ for *N*-desmethyl enzalutamide after a single oral dose is approximately 7.8–8.6 days [32]. Enzalutamide is primarily eliminated by hepatic metabolism [32].

3.3 Clinical Study: Interactions with P-gp and BCRP

In vitro DDI studies have indicated that enzalutamide is an inhibitor of P-gp and BCRP [34], and it has been suggested to have the potential for transporter-mediated DDIs via interactions with P-gp and BCRP when coadministered to

Table 2 Types of DDIs

Metabolic PK interactions	Inhibition of a metabolic enzyme that metabolizes a drug (e.g., CYP) can lead to an increased blood concentration of the drug Alternatively, metabolic enzyme induction may lead to a decreased drug blood concentration Inhibition of a metabolic enzyme that converts a prodrug to its active form may lead to decreased blood concentration of the active drug [13, 14] Alternatively, metabolic enzyme induction may lead to increased conversion of the prodrug to its active form and increased blood concentration of the active drug [13, 14]
Drug–transporter PK interactions	Inhibition of a transporter that promotes drug efflux (e.g., BCRP or P-gp) leads to increased drug concentration, whereas transporter induction leads to decreased plasma drug concentrations
Plasma protein PK DDIs	Competitive binding can lead to drug displacement from a carrier protein and alter the free active drug concentration
Absorptive PK DDIs	Intragastric pH influences the solubility and bioavailability of a drug
Pharmacodynamic interactions	Caused by the additive effects of two or more drugs (e.g., interaction of two agents that prolong the QTc interval)

BCRP breast cancer resistance protein, *CYP* cytochrome P450, *DDI* drug–drug interaction, *DPP4* dipeptidyl-peptidase 4, *P-gp* P-glycoprotein, *PK* pharmacokinetic, *QTc* QT corrected for heart rate

patients with medications that are substrates of these efflux transporters [35]. In addition, enzalutamide could potentially induce P-gp and BCRP as it is a strong inducer of CYP3A4 and because both transporters and CYP3A4 are induced by PXR [22, 24, 36]. To test the effects of enzalutamide on P-gp and BCRP, a phase I, open-label, placebo-controlled, fixed-sequence, crossover DDI study was conducted in men with metastatic CRPC [35]. The objective of this study was to measure the effects of enzalutamide on the pharmacokinetics of a transporter-probe cocktail containing the P-gp and BCRP substrates, digoxin and rosuvastatin [35]. Concomitant administration of enzalutamide with the P-gp substrate digoxin resulted in increased digoxin exposure (area under the curve [AUC] and plasma maximum concentration [C_{max}] of digoxin increased by 33% and 17%, respectively), suggesting that enzalutamide is a "mild" inhibitor of P-gp [35]. No pharmacokinetic interactions were observed between enzalutamide and rosuvastatin, suggesting that enzalutamide had no effect on BCRP in the men studied [35]. The authors concluded that enzalutamide-mediated induction of CYP2C9, CYP2C19, and CYP3A4 does not necessarily predict the overall effect on P-gp and BCRP, and that concomitant administration of enzalutamide with medications that are P-gp and BCRP substrates may not require dose adjustment [35]. The US prescribing information for enzalutamide was updated in September 2022 based on the results of this study [6].

3.4 Use of Enzalutamide in Special Populations

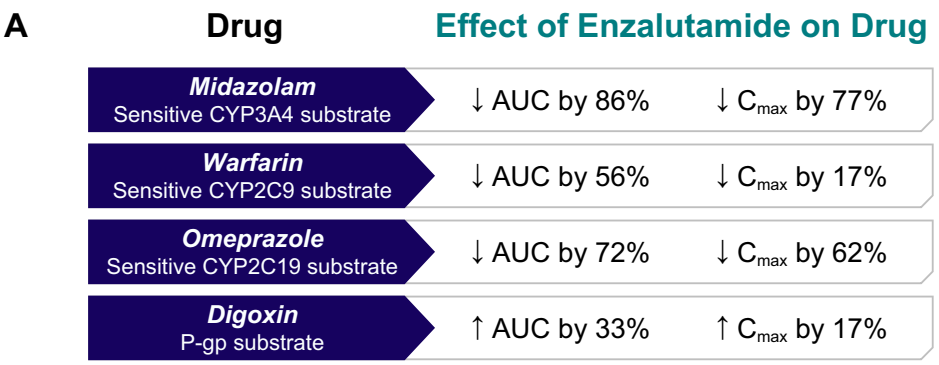
No overall differences in safety and effectiveness have been observed between patients aged <75 years and those aged ≥75 years treated with enzalutamide in clinical trials [37, 38]. No dosage modification is required in patients with mild-to-moderate renal impairment. Of note, enzalutamide has not been studied in severe/end-stage renal disease [32]. No dosage modification is required in mild, moderate, or severe hepatic impairment [6].

3.5 Enzalutamide and DDIs

More than 50% of older men with prostate cancer have one or more chronic comorbid conditions [39]. Polypharmacy is prevalent among elderly patients [5] and DDIs are an important consideration for clinical use of enzalutamide [6].

Enzalutamide reduced plasma exposure to drugs that are substrates of CYP2C9, CYP2C19, and especially CYP3A4 at steady state [6, 33]. Examples of drugs with concentrations reduced by enzalutamide include midazolam, warfarin, and omeprazole [33] (Fig. 1A). Specifically, enzalutamide decreased the AUC for midazolam by 86%, for warfarin by 56%, and for omeprazole by 72%. In general, coadministration of enzalutamide should be avoided with CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate [33]. It is possible for enzalutamide to have DDIs that do not cause meaningful clinical outcomes [40]. For example, enzalutamide may decrease the plasma concentration of a coadministered drug without decreasing the efficacy of that drug. Alternatively, enzalutamide may increase the exposure of a coadministered drug without affecting the adverse event profile of that drug. These scenarios are more likely when enzalutamide is coadministered with drugs that have a high therapeutic index. Risks of adverse events due to DDIs are primarily associated with narrow therapeutic index drugs for which a small change in the enzalutamide concentration could have a meaningful clinical outcome [33].

Coadministered drugs can also impact the concentration of enzalutamide and its active metabolite *N*-desmethyl



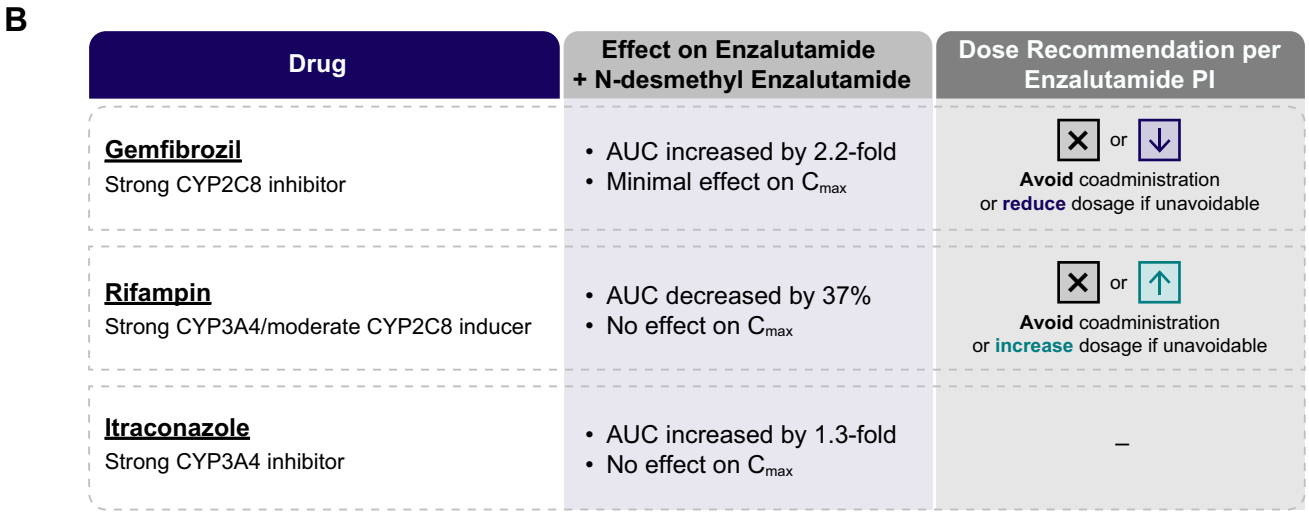


Fig. 1 Enzalutamide clinical drug interaction studies. Enzalutamide is metabolized by CYP2C8 and CYP3A4. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Enzalutamide was shown to be a mild inhibitor of human P-gp. *AUC* area under the curve (systemic drug exposure), C_{max} maximum concentration after a single dose, *CYP* cytochrome P450, *P-gp* P-glycoprotein, *PI* prescribing information

enzalutamide. Enzalutamide is metabolized by CYP2C8 and CYP3A4 [33]; therefore, coadministration of enzalutamide with drugs that either induce or inhibit these enzymes can alter enzalutamide concentrations. Gemfibrozil is an example of a strong CYP2C8 inhibitor and rifampin is an example of a strong CYP3A4/moderate CYP2C8 inducer (Fig. 1B). Gemfibrozil increased the AUC of enzalutamide plus *N*-desmethyl enzalutamide by 2.2-fold, while rifampin decreased the AUC by 37%. To mitigate the risk to patients, it is recommended to avoid coadministration of enzalutamide with a strong CYP2C8 inhibitor. However, if coadministration is unavoidable, use enzalutamide 80 mg once daily during concomitant use with a strong CYP2C8 inhibitor [33]. The dose of enzalutamide should be increased to 240 mg once daily for patients taking strong CYP3A4 inducers [6]. Additional examples of strong CYP3A4 inducers in addition to rifampin include carbamazepine, phenobarbital, and phenytoin [41].

In summary, enzalutamide can decrease the concentration of coadministered drugs that are substrates of CYP3A4, CYP2C9, or CYP2C19. It can also increase the concentration of drugs, such as digoxin, that are substrates of P-gp. Furthermore, coadministration of enzalutamide with drugs that are strong CYP2C8 inhibitors can increase enzalutamide plasma concentrations, whereas coadministration of enzalutamide with drugs that are strong CYP3A4 inducers can result in decreased enzalutamide blood concentrations. Prescribers should refer to the prescribing information of the medications being administered concomitantly with enzalutamide to assess the need to adjust medication doses based on the degree of potential CYP or transporter effects. However, prescribing information may not always be sufficient to fully account for a DDI and its management. Indeed, DDIs with a new drug may not be included in the prescribing information until revision. Therefore, in addition to referring to drug

interaction checkers such as those provided by Drugs.com and UpToDate (Lexicomp), it is also important to contact the pharmacovigilance unit and other specialists (e.g., cardiologists) to help identify and manage DDIs. In general, the combined expertise provided by multidisciplinary teams of physicians and other healthcare practitioners can substantially improve the management of complex treatment-related decisions and improve patient outcomes [42].

4 Enzalutamide with Specific Medication Classes

4.1 Patients With Prostate Cancer Are Commonly Treated for Various Comorbidities

Comorbidities that coexist in patients with prostate cancer over 65 years of age include hypertension, hypercholesterolemia, diabetes, cardiovascular diseases, chronic back pain, depression and anxiety, and others [43]. Therefore, patients with prostate cancer are commonly treated with drugs for a variety of other conditions and these need to be carefully managed together with medications aimed at treating their prostate cancer. Here, we describe potential DDIs between enzalutamide and other commonly prescribed drugs (Table 1) and frequently used supplements among patients with prostate cancer. We also propose strategies for preventing potentially problematic enzalutamide DDIs.

4.2 Oral Androgen Deprivation Therapy

Enzalutamide is prescribed in combination with androgen deprivation therapy (ADT) [26]. Commonly prescribed ADT drugs include the GnRH agonists leuprolide, goserelin, and triptorelin, and the GnRH antagonist degarelix [44]. These drugs are delivered via injection, are not metabolized via hepatic CYPs, and are not predicted to interact with enzalutamide [9]. Relugolix is an orally administered GnRH antagonist ADT that suppresses testosterone production in the treatment of prostate cancer [44]. Relugolix is a substrate of CYP3A, CYP2C8, and P-gp, and an inducer of CYP3A and CYP2B6 [45]. As enzalutamide is a mild P-gp inhibitor [35], it could increase the plasma concentration of P-gp substrates such as relugolix. However, enzalutamide is a strong inducer of CYP3A4, providing a mechanism through which it could potentially decrease the plasma concentration of relugolix. The HERO study demonstrated that relugolix suppresses testosterone in a manner superior to that of leuprolide in men with advanced prostate cancer [46]. In a subgroup and pharmacokinetic/pharmacodynamic analysis of the HERO study, George et al. demonstrated that treatment of patients with advanced prostate cancer with relugolix was associated with similar efficacy and safety outcomes with and without coadministration of enzalutamide [47]. Importantly, the results of this study suggest that any effects enzalutamide may have on relugolix metabolism do not have an overall impact on relugolix drug exposure or relugolix-mediated testosterone suppression [47]. Therefore, when enzalutamide is combined with relugolix, no dose adjustments are needed for either medication.

4.3 Enzalutamide and Agents Used to Treat Cardiovascular Diseases

Cardiovascular diseases are highly prevalent among patients with prostate cancer, especially those who are over 65 years of age [48]. Therefore, drugs used to treat and/or prevent cardiovascular disease will frequently need to be managed in patients over 65 years of age, including those with prostate cancer [49]. These include antithrombotic agents, statins, antihypertensive agents, antiarrhythmic agents, and drugs used to treat heart failure (HF).

4.3.1 Antithrombotic Agents

Anticoagulants and antiplatelet agents are critical for the prevention of thrombosis, which is the leading cause of all-cause death worldwide [50, 51]. However, a serious challenge posed by these drugs is the side effect of bleeding and this can be exacerbated by drug interactions.

4.3.1.1 Anticoagulants Anticoagulant agents are primarily used for the treatment or prevention of venous or arterial thromboses [51]. They inhibit the coagulation cascade and thrombus formation by inhibiting factor Xa (FXa) or thrombin [51].

4.3.1.2 Direct Oral Anticoagulants Direct oral anticoagulants (DOACs) are antithrombotic drugs that include apixaban, rivaroxaban, edoxaban, and dabigatran (Fig. 2). Apixaban, rivaroxaban, and edoxaban inhibit FXa, whereas dabigatran inhibits thrombin [51]. Apixaban and rivaroxaban are subject to potential DDIs by dual inhibitors and inducers of CYP3A4 and P-gp [52]. The effect of enzalutamide on the plasma concentration of these drugs is unclear because of opposing CYP3A4 and P-gp interactions. However, as enzalutamide is a strong CYP3A4 inducer and a mild P-gp inhibitor, its effects on CYP3A4 may be expected to be predominant resulting in a potential decrease in apixaban and rivaroxaban plasma concentrations, and therapy modification should be considered. Otsuka et al. [53] integrated in vitro and in vivo data into a physiologically based pharmacokinetic model to predict the extent to which

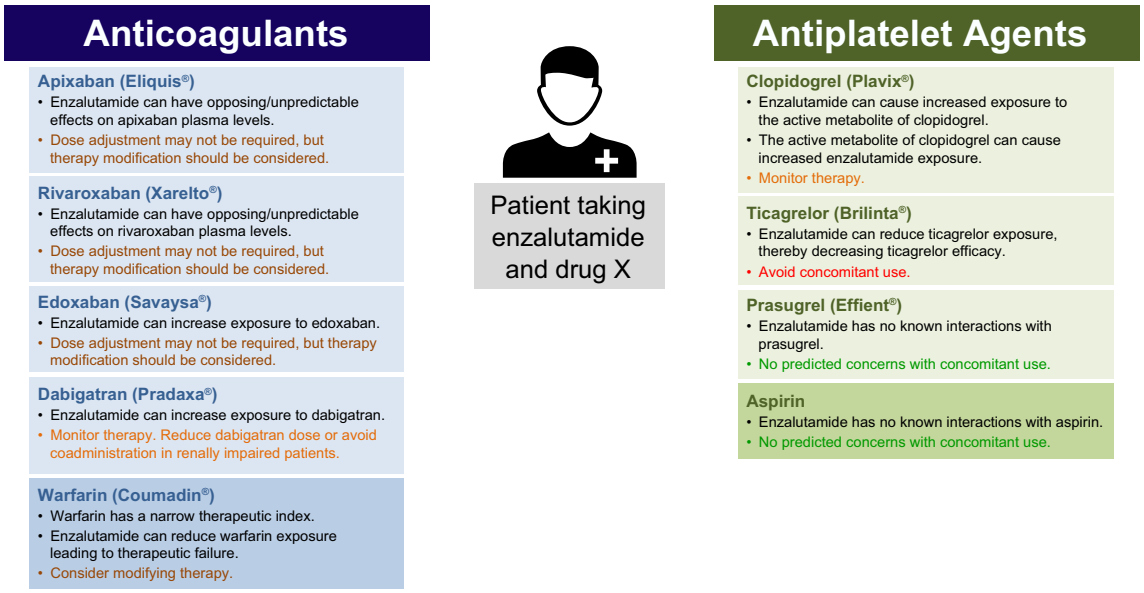


Fig. 2 Enzalutamide with anticoagulants and antiplatelet agents

enzalutamide and its active metabolite, *N*-desmethyl enzalutamide, impact apixaban and rivaroxaban plasma concentrations. The results predicted a 31% decrease in AUC and no change in C_{max} for apixaban and a 45% decrease in AUC and a 25% decrease in C_{max} for rivaroxaban following coadministration of the clinically relevant dose of 160 mg of enzalutamide [53]. Based on this study and current prescribing information, coadministration of these DOACs with enzalutamide should be carefully monitored with possible changes to dosing as necessary to ensure that drug efficacy and safety are maintained. Dabigatran and edoxaban are only minimally metabolized by CYPs and are only subject to DDIs by inhibitors and inducers of P-gp [52]. As enzalutamide was reported to be only a mild inhibitor of P-gp in human studies [35], any potential for DDIs with dabigatran and edoxaban may be less than for apixaban and rivaroxaban. However, concomitant use of P-gp inhibitors in renally impaired patients can increase the exposure of dabigatran, in which case the dabigatran dose should be reduced or coadministration should be avoided [54]. Dosing of dabigatran with enzalutamide should be based on the indication and level of renal dysfunction and we recommend that a pharmacist should be consulted to assist with the appropriate dose reduction of dabigatran or to determine if use of another DOAC is warranted.

4.3.1.3 Warfarin Warfarin is a vitamin K antagonist that blocks the coagulation cascade and thrombus formation by inhibiting thrombin [51]. Warfarin is a narrow therapeutic index medication that is a substrate of CYP2C9 and CYP3A4 [55]. As enzalutamide is a strong CYP3A4 inducer and moderate CYP2C9 inducer, it also has the potential to decrease the effect of warfarin (decrease international normalized ratio [INR]) by decreasing the exposure of warfarin. Coadministration of enzalutamide and warfarin should be avoided if possible or additional INR monitoring should be conducted if coadministration of these two drugs is unavoidable (Fig. 2).

4.3.1.4 Antiplatelet Agents Antiplatelet agents primarily prevent arterial thrombus formation by disrupting the platelet cascade [51].

4.3.1.5 P2Y12 Inhibitors Clopidogrel, prasugrel, and ticagrelor inhibit platelet activation by blocking platelet P2Y12 adenosine receptors [51]. These agents are commonly used to protect against strokes and heart attacks [56]. They also play an important role together with aspirin in dual antiplatelet therapy (DAPT) after coronary stent placement to prevent stent thrombosis/restenosis [57–59]. Although DAPT has proven to be successful in preventing stent thrombosis/restenosis, the benefits of prolonged DAPT must be carefully balanced against an increased bleeding risk [60]. Notably, it is important for patients to coordinate changes in DAPT with their cardiologist as switching between different P2Y12 inhibitors can be challenging because of their different potencies, half-lives, and the need for specific and appropriate loading doses [61]. If not done correctly, these changes can result in stent thrombosis, which can be fatal.

Clopidogrel and ticagrelor have known interactions with enzalutamide (Fig. 2). Clopidogrel is a prodrug that relies on CYP2C19 for conversion to its active metabolite [14]

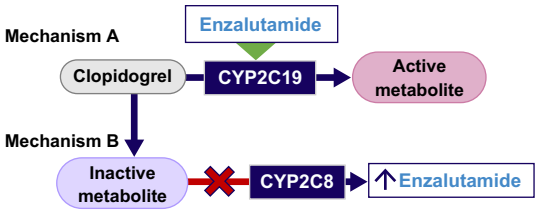


Fig. 3 Complex interactions between enzalutamide and clopidogrel. *CYP* cytochrome P450

(Fig. 3). Clopidogrel is also converted to an inactive acyl-β-glucuronide metabolite that is a time-dependent inhibitor of CYP2C8 [62]. Clopidogrel interacts with enzalutamide via two distinct mechanisms (Fig. 3): (1) enzalutamide can induce CYP2C19 and therefore has the potential to increase serum exposure to the active metabolite of clopidogrel; (2) as CYP2C8 is the primary enzyme responsible for metabolizing enzalutamide, clopidogrel has the potential to increase enzalutamide exposure. Because the inactive metabolite of clopidogrel is a strong CYP2C8 inhibitor, the prescribing information for clopidogrel recommends a dose adjustment and appropriate monitoring of drugs that are primarily cleared by CYP2C8 [63]. The prescribing information for enzalutamide also states that it should not be coadministered with strong CYP2C8 inhibitors [6]. However, in gauging the real effect of CYP2C19 induction on the amount of active metabolite formed, it is important to note that only ~15% of clopidogrel is converted to its active metabolite [14], and dose adjustments are not provided for enzalutamide for use with moderate CYP2C8 inhibitors [6]. In summary, coadministration of clopidogrel and enzalutamide should be carefully considered and if both drugs are coadministered, patients should be carefully monitored for increased pharmacologic effects of both medications. Ticagrelor is primarily metabolized via CYP3A4 and its plasma concentration may be reduced upon coadministration with strong CYP3A4 inducers [64], such as enzalutamide. Coadministration of ticagrelor with strong CYP3A4 inducers, such as enzalutamide, may reduce the exposure and efficacy of ticagrelor and should be avoided [64]. In contrast to clopidogrel and ticagrelor, prasugrel is only a minor substrate of CYP3A4 and has no known interactions with enzalutamide [9] (Fig. 2).

4.3.1.6 Aspirin Aspirin (ASA) is an irreversible inhibitor of cyclo-oxygenase 1 that reduces the production of thromboxane within platelets, thereby inhibiting platelet aggregation and thrombus formation. Low-dose ASA (81 mg/day) can be effective at preventing heart attacks and strokes [65]. In addition to its role in DAPT, mentioned above, most clinicians consider ASA to be critical for secondary prevention of myocardial infarction (MI) and atherosclerotic cardiovascular disease [66]; many patients with prostate cancer will have already had either stroke, MI, or coronary artery disease (CAD), which warrant ASA treatment. Fortunately, ASA does not have known interactions with enzalutamide [9] (Fig. 2).

4.3.2 Statins

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors used for the treatment of hypercholesterolemia, with high efficacy in reducing plasma low-density lipoprotein (LDL) and triglyceride levels [67]. Atorvastatin is a substrate of CYP3A4 and the transporters P-gp and BCRP [68], whereas simvastatin [69] and lovastatin [70] are primarily substrates of CYP3A4. Therefore, each of these drugs has potential for an interaction with enzalutamide [9]. Fluvastatin is primarily metabolized by CYP2C9 [71]. As enzalutamide is a moderate inducer of CYP2C9, it can also potentially interact with fluvastatin [9] with the potential to reduce fluvastatin exposure. Therefore, liver function and lipid levels should be monitored when statins are coadministered with enzalutamide to assess the safety and efficacy of statins. This should include checking a patient's lipid panel at baseline before starting statin therapy or adjusting statin dosage levels during therapy and conducting additional monitoring every 6–8 weeks to assess the treatment response. If lipid control is satisfactory with no evidence of adverse events, subsequent lipid monitoring can be conducted every 4–6 months [72]. However, atorvastatin (revised 11/2021), simvastatin (revised 05/2022), and fluvastatin (revised 10/2012) product recommendations do not preclude coadministration or provide dose adjustment recommendations [68, 69, 71]. The BCRP substrates, pitavastatin, pravastatin, and rosuvastatin, are preferred statins for patients who take enzalutamide as these statins are minimally metabolized by CYPs [73] and either have a moderate or no known basis for interaction with enzalutamide [9]. Of these three statins, rosuvastatin should be emphasized in particular as it is also a high-intensity statin and was shown to reduce LDL levels to a greater extent than atorvastatin, simvastatin, and pravastatin [74]. At the highest dose of 40 mg, rosuvastatin reduced LDL levels by 55% compared with 51% for atorvastatin 80 mg and 46% pravastatin 80 mg [74].

4.3.3 Antihypertensive Agents

Calcium (Ca) channel blockers (e.g., amlodipine, diltiazem, verapamil, and others) are frequently prescribed to decrease blood pressure in patients with hypertension [75]. Most Ca channel blockers are metabolized by CYP3A4 [76]. As enzalutamide is a potent inducer of CYP3A4 [6, 33], there is a potential for a DDI where enzalutamide may decrease the plasma concentrations of many Ca channel blockers [6, 33]. Concomitant use of Ca channel blockers, such as

amlodipine, with strong CYP3A4 inducers, such as enzalutamide, should be carefully considered [77]. If coadministration is necessary, the pharmacologic response of the Ca channel blocker should be monitored closely following the initiation or discontinuation of enzalutamide, and its dosage adjusted as necessary. If a patient requires treatment for hypertension, an angiotensin-converting enzyme (ACE) inhibitor, such as benazepril [78], which has no known interactions with enzalutamide [9], may be preferable to a Ca channel blocker. Beta-blockers, such as carvedilol, are also used to treat hypertension [79] and may also be preferable as they are not known to have interactions with enzalutamide [9].

4.3.4 Antiarrhythmic Agents

ADT has the potential to prolong the QT corrected for heart rate (QTc) interval and therefore the benefit–risk ratio of coadministration of enzalutamide with drugs known to prolong the QTc interval and/or induce Torsade de Pointes such as Class IA (e.g., disopyramide, quinidine, and procainamide) or Class III (e.g., amiodarone, dofetilide, and sotalol) antiarrhythmic agents [80] should be carefully considered [8]. However, in clinical practice, we only avoid prescribing enzalutamide if the patient has prolonged QTc or if the pharmacist raises a specific concern about a particular medication. In our opinion, potential risks of DDIs with enzalutamide and other drugs known to prolong the QTc interval can be safely overcome for most patients through multidisciplinary monitoring of serial electrocardiograms (EKGs) and ensuring that electrolytes are carefully managed. In this regard, we note that when the effects of enzalutamide 160 mg/day were evaluated in 796 men with CRPC, no large differences in the QTc interval caused by enzalutamide were observed [34]. Digoxin is a muscarinic M2 receptor activator Class IID antiarrhythmic drug [80] that is commonly prescribed for arrhythmia. As discussed above, digoxin is a P-gp substrate and coadministration of enzalutamide with digoxin increased digoxin exposure leading to the designation of enzalutamide as a mild P-gp inhibitor [35]. Poondru et al. concluded that dose modifications would most likely not be needed upon coadministration of enzalutamide and digoxin [35].

4.3.5 Other Heart Medications

Valsartan is an angiotensin type II receptor antagonist that blocks vasoconstriction [81]. Sacubitril is a prodrug that is activated to become a neprilysin inhibitor that reduces blood volume [82]. The combination of valsartan and sacubitril constitutes an important treatment for patients with heart failure [83]. These drugs do not have known interactions with enzalutamide [9]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are effective antidiabetic therapies, as discussed below, but also have significant cardiovascular benefits via mechanisms independent of improved glycemic control that are being intensively investigated [84]. SGLT2 inhibitors also do not have known interactions with enzalutamide (see below). Another important medication class in HF are mineralocorticoid receptor antagonists, which include spironolactone and eplerenone [85]. These drugs are both similarly effective in treating patients with congestive HF. However, eplerenone is primarily metabolized by CYP3A4 and it has been reported that St John's Wort, a CYP3A4 inducer, may reduce eplerenone concentrations by 30% [85]. Therefore, while spironolactone and enzalutamide are not anticipated to have drug interactions, there is potential for an interaction between enzalutamide and eplerenone [9].

4.4 Antidiabetic Agents

Together with cardiovascular diseases, diabetes is highly prevalent among patients with prostate cancer over the age of 65 years [48]. Sulfonylureas, including glyburide, gliclazide, and glimepiride, are frequently used hypoglycemic agents for the treatment of type 2 diabetes [86, 87]. These antidiabetic drugs are primarily metabolized by CYP2C9 [87] and therefore, there may be potential for a DDI and susceptibility to reduced plasma concentrations upon coadministration with enzalutamide, a moderate CYP2C9 inducer. Dipeptidyl-peptidase 4 (DPP4) inhibitors, such as saxagliptin, are also used to treat type 2 diabetes [88]. Saxagliptin is primarily metabolized by CYP3A4/5 [88] and, therefore, there may be potential for a DDI and increased risk for reduced drug efficacy when coadministered with enzalutamide, a strong CYP3A4 inducer. One effective alternative to these drugs is metformin, a widely prescribed medication for type 2 diabetes with no known interactions with enzalutamide [9]. SGLT2 inhibitors are also effective in treating type 2 diabetes and, importantly, they are not metabolized by CYPs that are induced by enzalutamide [89] and are not known to have interactions with enzalutamide.

4.5 Antidepressants

Depression is common among elderly patients, particularly those with cancer [90]. Citalopram is a commonly prescribed serotonin-selective reuptake inhibitor (SSRI) antidepressant medication that can cause dose-dependent prolongation of the QTc interval [91]. Therefore, coadministration of ADT/enzalutamide together with citalopram should be carefully considered to avoid risk of prolonged QTc and Torsade de Pointes. However, as discussed above, it should be possible to overcome potential QTc issues in most patients through careful multidisciplinary monitoring of serial EKGs and ensuring that electrolytes are carefully

managed. Fluoxetine and sertraline are additional SSRIs that can also lengthen the QTc interval but to a lesser degree than citalopram [92]. Therefore, these two drugs are predicted to have more moderate DDI risks with enzalutamide compared with citalopram [9].

Serotonin and norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, desvenlafaxine, and duloxetine) may be preferable alternatives to SSRIs for the treatment of depression in patients with prostate cancer who are also being treated with enzalutamide, as SNRIs have a low risk for QTc prolongation [93, 94]. While venlafaxine can prolong the QTc interval and may pose a moderate risk when coadministered with enzalutamide, no significant risk of QTc prolongation was observed for duloxetine [94], and neither desvenlafaxine nor duloxetine have known interactions with enzalutamide [9].

4.6 Antiseizure Medications

Several antiseizure medications including carbamazepine, phenobarbital, phenytoin, and primidone (partially metabolized to phenobarbital) are potent CYP2C9 and/or 3A4 inducers [41]. As enzalutamide is metabolized by CYP3A4, there is potential for a DDI and plasma concentrations may be decreased if enzalutamide is coadministered with these drugs. Therefore, if concomitant use of enzalutamide and these drugs cannot be avoided the enzalutamide dosage should be increased from 160 mg to 240 mg once daily [6]. If the interacting antiseizure medication is discontinued, the original enzalutamide dose of 160 mg once daily can be re-established. Valproic acid, lamotrigine, gabapentin, and topiramate are alternative antiseizure medications that do not have known interactions with enzalutamide [9].

4.7 Common Urology Medicines

Oxybutynin is a commonly prescribed antimuscarinic agent that is used to treat overactive bladder (OAB) [95]. Because of its anticholinergic properties, oxybutynin should be used with caution in elderly patients owing to its potential negative effect on cognitive function [96]. Oxybutynin is primarily metabolized by CYP3A4 [97], which is strongly induced by enzalutamide. Therefore, there is potential for a DDI that may result in decreased plasma concentrations of oxybutynin if coadministered with enzalutamide. Mirabegron is also used to treat OAB [95] and may similarly interact with enzalutamide [9]. Trospium is a potentially preferable alternative to oxybutynin and mirabegron for the treatment of OAB as it has no known interactions with enzalutamide [9]. Tamsulosin is a commonly prescribed alpha adrenergic receptor blocker used to treat enlarged prostate and difficulty urinating [98]. Tamsulosin is also metabolized by CYP3A4 and therefore there is potential for a DDI if coadministered with enzalutamide, which may potentially cause reduced tamsulosin serum exposure [9].

4.8 Pain Medications

Enzalutamide coadministration with oxycodone, methadone, tramadol, and fentanyl may result in decreased plasma concentration of these opioid analgesics as they are primarily metabolized by CYP3A4 [99], which is strongly induced by enzalutamide. It was recently shown that enzalutamide decreases exposure to oxycodone and its active metabolite oxymorphone [100]. This interaction is clinically relevant as pain may not be adequately controlled when both drugs are present and there is a risk of overdose upon enzalutamide discontinuation [100]. Enzalutamide coadministration with these opioids should be monitored closely. In particular, the pharmacologic response to the opioid should be checked regularly when enzalutamide is added to or withdrawn from therapy, and the opioid dosage should be adjusted as necessary. Morphine, hydromorphone, and oxymorphone are preferable alternatives as they are not metabolized by CYPs [99] and have no known interactions with enzalutamide [9].

4.9 Proton Pump Inhibitors (PPIs)

PPIs inhibit stomach acid production and treat common acid-related disorders including heartburn, ulcers, and gastroesophageal reflux disease [101]. There are currently six PPIs available: omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, and pantoprazole [101]. Omeprazole, esomeprazole, lansoprazole, and rabeprazole are primarily metabolized by CYP2C19, whereas dexlansoprazole and pantoprazole are metabolized by CYP2C19 and CYP3A4 [101]. Coadministration of enzalutamide 160 mg once daily with omeprazole decreased omeprazole AUC by 70% and C_{max} by 62% [6] (Fig. 1A). However, product recommendations do not preclude coadministration or provide dose-adjustment recommendations [102] and clinical discretion is advised. Dexlansoprazole, which is the R-enantiomer of lansoprazole, is a highly efficacious delayed-release PPI with safety and side-effect profiles that are similar to lansoprazole [103]. Dexlansoprazole is the preferred PPI for coadministration with enzalutamide as it has no known drug interactions, whereas the other five available PPIs have the potential for moderate interactions [9]. Notably, the solubility of enzalutamide is not affected by pH over the physiological range [32] and, therefore, PPIs are not expected to alter enzalutamide absorption.

4.10 Immunosuppressants

Commonly used immunosuppressants include cyclosporine, tacrolimus, everolimus, and sirolimus [104]. Cyclosporine can inhibit CYPs that metabolize enzalutamide and, therefore, it has the potential to increase the plasma concentration of enzalutamide [9]. Tacrolimus, everolimus, and sirolimus are metabolized by CYP3A4 [104], and their plasma concentrations can be decreased by enzalutamide potentially resulting in a loss of clinical efficacy [9].

4.11 Antigout Drugs

Gout is an inflammatory disease caused by build-up of uric acid in joints. Painful flare-ups can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., naproxen sodium), or prednisone, whereas uric acid accumulation can be ameliorated by treatment with allopurinol [105]. As colchicine and prednisone are metabolized by CYP3A4, and naproxen sodium is metabolized by CYP2C8 and CYP2C9, the plasma concentrations of each of these drugs have the potential to be decreased by enzalutamide [9]. No DDIs are predicted between enzalutamide and allopurinol [9].

4.11.1 Supplements

The use of complementary and alternative medicines is highly popular among patients with cancer. It is estimated that approximately three quarters of patients with cancer who use alternative medicines in addition to their conventional cancer therapies do not inform their treating physician [106]. One of the best characterized examples of an alternative medicine with clinically significant drug interactions is St. John's Wort, which is used to treat mild-to-moderate depression [106]. St John's Wort induces CYP3A4 [106] and therefore has the potential to decrease the plasma concentration of enzalutamide, a CYP3A4 substrate. Coadministration of St John's Wort with enzalutamide should generally be avoided. Mushroom-derived supplements including lion's mane, maitake, reishi, and turkey tail have been reported to have anticancer properties [107] and are very popular among patients with cancer. A recent series of Cancer Information Summaries on Prostate Cancer, Nutrition, and Dietary Supplements from the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board [108] provided results on the interactions of foods and dietary supplements including Ca, green tea, lycopene, modified citrus pectin, pomegranate, selenium, soy, vitamin D, and vitamin E. Of these, there is evidence that green tea, modified citrus pectin, pomegranate, and soy are associated with a decreased risk of prostate cancer or beneficial effects for patients with prostate cancer [108]. There are no known drug interactions between enzalutamide and any of the following [9, 10]: lion's mane, maitake, reishi, turkey tail, cordyceps, Ca 600 D (Ca/vitamin D), green tea, Theratrum Complete 50 Plus with lutein and lycopene, pectin, Emergen-C cranberry-pomegranate (multivitamin with minerals), selenium, soya lecithin, vitamin D_2, vitamin E, or vitamin A. Turmeric and fish oil are also popular supplements that are not known to interact with enzalutamide [10]. These findings suggests that many popular supplements and vitamins may be safe to take together with enzalutamide, at least individually and at appropriate doses. However, the treating physician should always be made aware of all complementary and alternative medicines being taken by the patient so that their potential interactions with enzalutamide can be monitored.

5 Conclusions

Enzalutamide is a highly effective anti-androgen for the treatment of advanced prostate cancer [109]. However, it has potential risks of DDIs in certain situations. Enzalutamide interacts with key CYPs and transporters. It moderately induces CYP2C9 and CYP2C19 and strongly induces CYP3A4 [33]. Notably, CYP3A4 metabolizes approximately one third of drugs that are metabolized in the liver [110] and is the predominant source of enzalutamide DDIs. Therefore, by inducing CYP3A4, there is a potential for DDIs when enzalutamide is coadministered with a broad range of drugs that are CYP3A4 substrates including certain anticoagulants and antiplatelet agents, statins, Ca channel blockers, antiarryhythmic agents, and many others (Table 1). It is important to understand this and the other mechanisms of enzalutamide DDIs as they may result in a loss of efficacy when coadministering with other drugs or an increased risk of drug-related adverse effects. Fortunately, where DDIs pose challenges, it may be possible to rationally alter dosing, particularly with the integrated expertise of a multidisciplinary team of experts, and there are often alternative drugs that can be used that do not interact with enzalutamide or which pose minor or moderate risks.

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