Prostate Cancer: Drugs and their side effects

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COI Declaration

TYPE OF AFFILIATION	NAME OF ORGANIZATION	DETAILS / DATE (from/to)
I am a member of an advisory board or similar committee for a for-profit or non-profit organization	TerSera Abbvie	May 26 2020 Oct 15 2020, Feb 25 2021
I have received payment from a for-profit or non-profit organization (including gifts, etc...)	TerSera	Travel funding to GU ASCO Conference 2020
I am currently participating in or have participated in a clinical trial within the past two years	Bristol-Myers Squibb	BCG and immunotherapy in non muscle invasive bladder cancer

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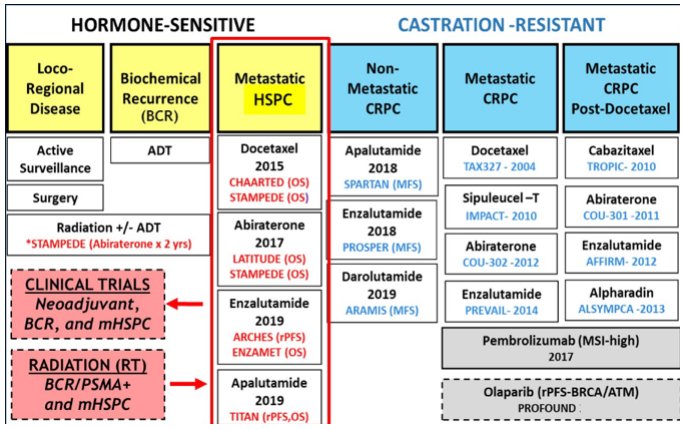
Learning Objectives – Anti Androgen Drugs and their side effects

-Overview of Prostate Cancer drugs: Focus on Anti-androgens
- -Non Steroidal Anti-Androgens
  - -Bicalutimide
- -Androgen Deprivation Therapy
  - -GnRH Antagonists
  - -LHRH Agonists
- -Androgen Receptor Antagonists
  - -Enzalutimide
  - -Apalutimide
- -CYP17 Inhibitor
  - -Abiraterone

Prostate Cancer Therapeutic Landscape



Adapted from: https://www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-prostate-cancer/119166-asco-gu-2020-treatment-selection-in-cspc-considerations-now-and-downstream-in-an-evolving-therapeutic-landscape-discussion-of-abstracts-82-and-162.html

Non Steroidal Anti-Androgens

- Competitive antagonists of androgen receptor
- NB: *Partial Agonists
- Bicalutimide/Casodex most commonly used
- ->50mg PO Daily
- ->Used to suppress testosterone flare from LHRH agonists
- ->Used in total androgen blockade (limited use currently)

Absorption	Oral: Well absorbed. Food does not appear to affect the rate or extent of absorption.	
Distribution	The (R)-enantiomer accumulates about 10-fold with daily administration.	
	Cross blood brain barrier?	Probably poor penetration
	PPB	> 96 %
Metabolism	Bicalutamide undergoes stereospecific metabolism, with hepatic biotransformation via glucuronidation and oxidation. The (S)-enantiomer is very rapidly cleared relative to the (R)-enantiomer.	
	Active metabolites	R-enantiomer
Elimination		
	Feces	43 % over 9 days
	Urine	36 % over 9 days
	Half-life	1 week

Cancer Care Ontario:
https://www.cancercareontario.ca/en/drugformulary/drugs/bicalutamide

Non Steroidal Anti-Androgens

- Side effects:
- Diarrhea (10%)
- Fatigue
- Gynecomastia and breast tenderness: more common in monotherapy (38%)
- Hot flashes: monotherapy (12%)
- Erectile function not significantly altered with bicalutamide monotherapy

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
LHRH analogues[21]	no interactions have been identified		
warfarin[10]	increased risk of bleeding	displacement of warfarin from protein binding sites	monitor INR with increased frequency when bicalutamide is being started or discontinued; adjust warfarin dose as needed.

Cancer Care Ontario: https://www.cancercareontario.ca/en/drugformulary/drugs/bicalutamide
BC Cancer Agency: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bicalutamide_monograph_1October2011.pdf

Non Steroidal Anti-Androgens

Recommended Clinical Monitoring

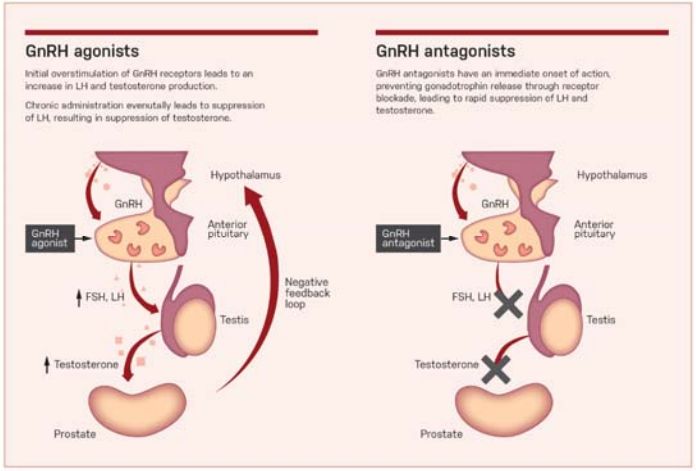
Monitor Type	Monitor Frequency
Liver function tests	baseline and regular
Electrolytes	baseline, also during treatment for patients at risk of electrolyte abnormality and QT prolongation
Blood glucose	especially in diabetic patients; baseline and regular
ECG	baseline; also during treatment for patients at risk of QT prolongation
Bone density	as clinically indicated
INR, for patients on warfarin	as clinically indicated
Clinical assessment for fluid retention, pneumonitis, androgen withdrawal effects, cardiovascular, hepatic effects and thromboembolism	at each visit

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Hemoglobin	baseline and as clinically indicated

Cancer Care Ontario:
https://www.cancercareontario.ca/en/drugformulary/drugs/bicalutamide

GnRH Antagonists and LHRH Agonist



https://www.urotoday.com/journal/everyday-urology-oncology-insights/articles/96381-assessment-of-cardiovascular-risk-with-the-use-of-androgen-deprivation-therapy-for-prostate-cancer-everyday-urology-full-text-article.html

LHRH Agonists

- LHRH Agonist mechanism of action:
- →Overactivation of hypothalamus-pituitary axis leads to suppression
- →Temporary spike in Testosterone seen: NB in patients with high volume PCa
- →Can block with NSAA

- Eligard (Leuprolide Acetate); 1/3/4/6 month depo injections
- Zoladex (Goserelin Acetate); 1/3
- Lupron (Leuprolide Acetate); 1/3/4/6
- Trelstar (Triptorelin); 1/3/6

GnRH Antagonists

- Direct GnRH Antagonist
- Degarelix/Firmagon
- →240mg SC loading dose
- →80mg SC q monthly
- Injection site reactions common
- Possibly lower risk of cardiovascular toxicity – ongoing area of research

PHARMACOKINETICS:

Distribution	rapid initially, then slowly due to depot formation[1,3]; higher concentration increases half-life and decreases Cmax[4]; time to peak 37-42 h	
	cross blood brain barrier?	no information found
	volume of distribution[3]	>1000 L
	plasma protein binding	~90%
Metabolism	hepatobiliary, via peptide hydrolysis[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	mainly excreted as peptide fragments in feces	
	urine[2]	20-30% (unchanged)
	feces[3]	70-80%
	terminal half life	starting dose: 43-53 days[1,2]; maintenance dose: 28 days
	clearance[4]	~9 L/h

BC Cancer: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Degarelix_monograph_1Feb2015.pdf

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CUAJ – CUA Guideline

Kokorovic et al
Guideline: ADT

Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies

Andrea Kokorovic, MD[1]; Alan I. So, MD[2]; Hosam Serag, MD[2]; Christopher French, MD[3]; Robert J. Hamilton, MD[4]; Jason P. Izard, MD[5]; Jasmir G. Nayak, MD[6]; Fréderic Pouliot, MD[7]; Fred Saad, MD[1]; Bobby Shayegan, MD[8]; Armen Aprikian, MD[9]; Ricardo A. Rendon, MD[10]

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https://www.cua.org/system/files/Guidelines/7355_Guideline_ADT_Epub.pdf

Summary of adverse events associated with androgen deprivation therapy

Complication	Summary of events	Management
Cardiovascular disease	Increased risk of cardiac events Increased risk of stroke Increased risk of DVT/PE	1. Lifestyle changes to promote healthy diet and weight 2. Smoking cessation 3. Exercise therapy 4. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles 5. Consider use of GnRH antagonist in patients with significant cardiac comorbidities 6. Consider referral to cardiac oncology
Change in body composition	Increased BMI Increased percentage body fat Decreased muscle mass	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Change in metabolic parameters	Insulin resistance/glucose intolerance Increased risk for incident diabetes Worse glycemic control Altered lipid profiles Increased risk for metabolic syndrome	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Bone health	Decreased BMD Increase risk for osteoporosis Incrased risk for clinical fractures	1. Smoking and alcohol cessation (all men) 2. Adequate calcium intake (1200 mg daily) and vitamin D supplementation (800-1000 IU daily) (all men) 3. Exercise therapy (all men) 4. Pharmacological therapy with a bisphosphonate or denosumab for men with risk factors for bone fracture (ie. previous history of low trauma fracture, diagnosis of osteoporosis, moderate or high 10-year fracture risk)
Hot flashes	Hot flashes	1. Avoidance of triggers 2. Pharmacological therapy 3. Consider acupuncture
Breast events	Gynecomastia Mastodynia	1. Treatment with tamoxifen or low dose RT (tamoxifen preferred) 2. Surgical management for select patients
Cognitive function	Concentration Memory Dementia	1. Evidence for causality is weak 2. Appropriate patient education and monitoring of symptoms
Fatigue and anemia		1. Exercise therapy for fatigue 2. Work up secondary causes of anemia and referral to hematology
Impaired sexual function	Decreased penile and testicular size Loss of libido Decreased sensitivity to sexual stimulation Erectile dysfuncton	1. Appropriate pre-treatment counselling 2. Sex therapy 3. PDE-5 inhibitor therapy where appropriate 4. Intermittent ADT
Quality of life	Multiple domains	1. Exercise therapy 2. Intermittent ADT where appropriate

https://www.cua.org/system/files/Guidelines/7355_Guideline_ADT_Epub.pdf

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ADT Side Effects

Complication	Summary of events	Management
Cardiovascular disease	Increased risk of cardiac events Increased risk of stroke Increased risk of DVT/PE	1. Lifestyle changes to promote healthy diet and weight 2. Smoking cessation 3. Exercise therapy 4. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles 5. Consider use of GnRH antagonist in patients with significant cardiac comorbidities 6. Consider referral to cardiac oncology
Change in body composition	Increased BMI Increased percentage body fat Decreased muscle mass	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Change in metabolic parameters	Insulin resistance/glucose intolerance Increased risk for incident diabetes Worse glycemic control Altered lipid profiles Increased risk for metabolic syndrome	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles

- Retrospective data:
- Cardiac Events HR 1.38 in retrospective study
- Cardiovascular mortality HR 1.17
- Highest risk among men with pre-exisiting CVD → Controversy regarding LHRH gonists vs GnRH Antagonists

https://www.cua.org/system/files/Guidelines/7355_Guideline_ADT_Epub.pdf

ADT Side Effects

Bone health	Decreased BMD Increase risk for osteoporosis Incrased risk for clinical fractures	1. Smoking and alcohol cessation (all men) 2. Adequate calcium intake (1200 mg daily) and vitamin D supplementation (800-1000 IU daily) (all men) 3. Exercise therapy (all men) 4. Pharmacological therapy with a bisphosphonate or denosumab for men with risk factors for bone fracture (ie. previous history of low trauma fracture, diagnosis of osteoporosis, moderate or high 10-year fracture risk)
Hot flashes	Hot flashes	1. Avoidance of triggers 2. Pharmacological therapy 3. Consider acupuncture
Breast events	Gynecomastia Mastodynia	1. Treatment with tamoxifen or low dose RT (tamoxifen preferred) 2. Surgical management for select patients

- Hot Flash Medications – NB None Health Canada Approved for this indication
- Venlafaxine (Effexor) 75 mg orally daily
- Medroxyprogesterone acetate (Provera) 20 mg orally daily
- Cyproterone acetate (Androcur) 100 mg orally daily
- Gabapentin (Neurontin) 900 mg orally daily
- Megestrol acetate (Megace) 20 mg orally twice daily

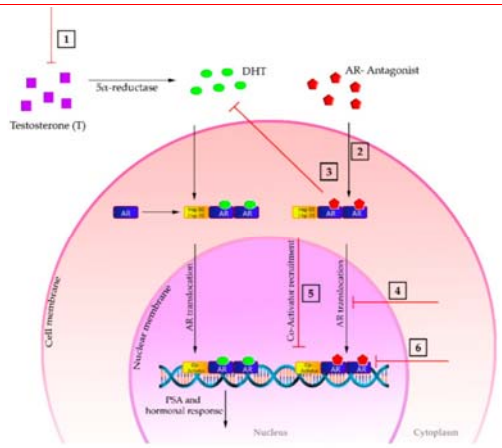
https://www.cua.org/system/files/Guidelines/7355_Guideline_ADT_Epub.pdf

ADT Side Effects

Cognitive function	Concentration Memory Dementia	1. Evidence for causality is weak 2. Appropriate patient education and monitoring of symptoms
Fatigue and anemia		1. Exercise therapy for fatigue 2. Work up secondary causes of anemia and referral to hematology
Impaired sexual function	Decreased penile and testicular size Loss of libido Decreased sensitivity to sexual stimulation Erectile dysfunction	1. Appropriate pre-treatment counselling 2. Sex therapy 3. PDE-5 inhibitor therapy where appropriate 4. Intermittent ADT
Quality of life	Multiple domains	1. Exercise therapy 2. Intermittent ADT where appropriate

https://www.cua.org/system/files/Guidelines/7355_Guideline_ADT_Epub.pdf

Androgen Receptor Antagonists



1. Suppresses testosterone production
- Surgical and Medical Castration Therapy
- Abiraterone acetate

2. Competitive binding to AR
- Bicalutamide*
- Enzalutamide
- Apalutamide
- Darolutamide

3. Prevents DHT-AR binding
- Bicalutamide*
- Enzalutamide
- Apalutamide
- Darolutamide

4. Blocks AR translocation to nucleus
- Enzalutamide
- Apalutamide
- Darolutamide

5. Impairs Co-Activator recruitment
- Enzalutamide
- Apalutamide
- Darolutamide

6. Restrains AR-DNA binding
- Enzalutamide
- Apalutamide
- Darolutamide

Rajaram P, Rivera A, Muthima K, Olveda N, Muchalski H, Chen QH. Second-Generation Androgen Receptor Antagonists as Hormonal Therapeutics for Three Forms of Prostate Cancer. Molecules. 2020 May 24;25(10):2448. doi: 10.3390/molecules25102448. PMID: 32456317; PMCID: PMC7287767.

Enzalutimide

- Enzalutimide
- First 2nd generation androgen receptor antagonists
- 80-160mg PO Daily

PHARMACOKINETICS:

Oral Absorption	rapid[3]; absorption estimated at 84%; food has no clinically significant effect on extent of absorption, however peak plasma concentration may be 30% higher when fasting	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	yes, including active metabolite
	volume of distribution	110 L
	plasma protein binding	parent (97-98%), primarily to albumin ; metabolites (95-98%)
Metabolism	extensively metabolized; substrate of CYP 2C8 and to a lesser extent CYP 3A4/5	
	active metabolite(s)	N-desmethyl enzalutamide (M2); primarily via CYP 2C8
	inactive metabolite(s)	carboxylic acid derivative (M1) primarily; up to 7 other unnamed phase I metabolites
Excretion	primarily via renal excretion of hepatic metabolites	
	urine	71% (primarily as M1; trace amounts of enzalutamide and M2)
	feces	14% (<1% as unchanged enzalutamide)
	terminal half life	5.8 days
	clearance	0.56 L/h (range 0.33 to 1.02 L/h)[4]
Elderly	no meaningful differences[4]	

Adapted from standard reference[3] unless specified otherwise.

BC Cancer: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Degarelix_monograph_1Feb2015.pdf

Enzalutimide

- Enzalutimide
- Most common: **Fatigue**, MSK pain, ↑lfts, diarrhea, androgen deprivation symptoms, edema, headache, **HTN**, dizziness, insomnia
- **Increased seizure risk**

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (11%) (may be severe)	E
	QT interval prolonged (rare)	E
Dermatological	Rash (4%) , dry skin	E
Gastrointestinal	Diarrhea (22%)	E
General	Edema (15%)	E
	Fall (4%)	E
	Fatigue (34%)	E
Hematological	Myelosuppression ± infection, bleeding (1%) (severe)	E
Hepatobiliary	↑ Bilirubin (3%) (incidence similar to placebo)	E
Musculoskeletal	Fracture (4%)	D
	Musculoskeletal pain (26%)	E
Nervous System	Anxiety (6%)	E
	Cognitive disturbance (5%)	E
	Dizziness (10%)	E
	Hallucinations (0.8%)	E
	Headache (12%)	E
	Insomnia (9%)	E
	Paresthesia (7%)	E
	RPLS / PRES (rare)	E
	Seizure (0.5%)	E
Reproductive and breast disorders	Androgen deprivation symptoms (20%)	E
Urinary	Urinary symptoms (7%)	E

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Enzalutamide_monograph_1Oct2015.pdf

Enzalutimide

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
gemfibrozil[2]	2 fold increase in AUC of enzalutamide	inhibition of CYP 2C8 by gemfibrozil	avoid concurrent use if possible; otherwise, a 50% dose reduction for enzalutamide is recommended
itraconazole[2]	1 fold increase in AUC of enzalutamide	inhibition of CYP 3A4 by itraconazole	monitor for side effects of enzalutamide; dose adjustment is not required
midazolam[2]	86% decrease in AUC of midazolam	induction of CYP 3A4 by enzalutamide	avoid concurrent use
omeprazole[2]	70% decrease in AUC of omeprazole	induction of CYP 2C19 by enzalutamide	avoid concurrent use
warfarin[2]	56% decrease in AUC of S-warfarin	induction of CYP 2C9 by enzalutamide	monitor INR; adjust dose of warfarin as needed

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Enzalutamide_monograph_1Oct2015.pdf

Enzalutimide

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline and at each visit
ECG and electrolytes	Baseline and at each visit, in patients at risk of QT prolongation
INR monitoring for patients on warfarin	Baseline and at each visit
Clinical toxicity assessment for androgen withdrawal effects, fatigue, seizures and other neuropsychiatric effects, falls, musculoskeletal and fractures, edema, diarrhea	at each visit

https://www.cancercareontario.ca/sites/ccocancercare/files/enzalutamide.pdf

Apalutimide

- Apalutimide/Erleada
- 2nd generation androgen receptor antagonist
- 120-240mg PO Daily

PHARMACOKINETICS:

Oral Absorption	bioavailability ~100%; time to peak: 2 h; steady state after 4 weeks	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	yes (based on animal studies)
	volume of distribution	276 L
	plasma protein binding	96% apalutamide; 95% N-desmethyl apalutamide
Metabolism	mainly by CYP 2C8 and CYP 3A4 (40% and 37%, respectively, at steady state)	
	active metabolite(s)	N-desmethyl apalutamide (44%)
	inactive metabolite(s)	carboxylic acid metabolite (3%)
Excretion	primarily by urinary excretion of inactive metabolites	
	urine	65% (1% unchanged apalutamide, 3% N-desmethyl apalutamide)
	feces	24% (2% unchanged apalutamide, 2% N-desmethyl apalutamide)
	terminal half life	~3 days at steady state
	clearance	2 L/h at steady state

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Apalutamide_monograph.pdf

Apalutimide

ORGAN SITE	SIDE EFFECT
	Clinically important side effects are in *bold, italics*
neutropenia	lymphopenia (41%, severe 2%)
cardiac	heart failure (2%)
	ischemic heart disease (4%)
	myocardial infarction (severe <1%)
endocrine	***hypothyroidism*** (8-22%)[2,9,10]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential* low[11]
	abdominal pain (18-30%, severe 2-3%)[8,10,12]
	constipation (15-23%, severe 4%)[8,12]
	diarrhea (20-43%, severe 1-2%)[2,8,10,12]
	flatulence (9%)[8]
	nausea (18-46%, severe 3%)[8,10,12]
	vomiting (≤17%, severe 2%)[8,9]
general disorders and administration site conditions	edema, peripheral (11-17%)[8,12]
	fatigue (30-61%, severe ≤4%)[2,8,10,12]
	pain (13%, severe 3%)[12]
infections and infestations	nasopharyngitis (16%)[8]
	pneumonia (severe 1%)
	sepsis (severe 1%)
	upper respiratory infection (11-16%)[8,10]
	urinary tract infection (severe 1%)
injury, poisoning, and procedural complications	***falls*** (16%, severe 2%)[2,8]; see paragraph following **Side Effects** table
	fracture (12%, severe 3%)[2,8]; see paragraph following **Side Effects** table
investigations	***hypercholesterolemia*** (76%, severe <1%)
	thyroid stimulating hormone increase (25%)[8]
	weight loss (16-18%, severe 1%)[8,10]
metabolism and nutrition	anorexia (12-20%)[8,9]
	hyperglycemia (70%, severe 2%)
	hyperkalemia (32%, severe 2%)
	hypertriglyceridemia (67%, severe 2%)
musculoskeletal and connective tissue	arthralgia (16-27%, severe 2-3%)[2,8,10,12]
	back pain (22-30%, severe 4%)[8,10,12]
	musculoskeletal chest pain (15%, severe 2%)[8]
	musculoskeletal pain (17%, severe 2%)[8,12]
	pain in extremity (17-20%, severe 2%)[10,12]

ORGAN SITE	SIDE EFFECT
	Clinically important side effects are in *bold, italics*
nervous system	cerebral hemorrhage (severe <1%)
	cerebrovascular accident (severe <1%)
	dizziness (13%)[8]
	dysgeusia (22%)[10]
	headache (15-20%)[8,12]
	peripheral sensory neuropathy (20%)[12]
	seizure (<1%)[2,8]; see paragraph following **Side Effects** table
psychiatric	insomnia (11%)[8]
renal and urinary	hematuria (16%)[10]
	pollakiuria (18%)[10]
	urinary tract hemorrhage (10%)[12]
respiratory, thoracic and mediastinal	cough (17-20%)[8,12]
	dyspnea (22-30%, severe 2%)[8,12]
skin and subcutaneous tissue	pruritus (6%)
	rash (15-24%, severe 5%)[2,8,9]; see paragraph following **Side Effects** table
vascular	hot flashes (11-20%)[2,8,10,12]
	hypertension (25%, severe 14%)[2,8]

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Apalutamide_monograph.pdf

Apalutimide

- Rash: up to 25%; some grade 3-4
- →median onset within 3 months
- →usually resolves within 2 months
- →recurs in up to 50% with rechallenge
- →treatment: corticosteroids and antihistamines
  +/- dose reduction/interruption/discontinuation

- Siezure: increased risk with apalutimide as well

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Apalutamide_monograph.pdf

Apalutimide

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
abiraterone and prednisone[4]	no effect on apalutamide or abiraterone kinetics		
fexofenadine[2]	30% decrease in fexofenadine AUC	weak induction of P-glycoprotein by apalutamide	monitor for reduced control of allergy symptoms; adjust fexofenadine dose as required
gemfibrozil[2]	19-32% increase in C_{max} and 23-44% increase in AUC of apalutamide	strong CYP 2C8 inhibition by gemfibrozil	initial dose adjustment is unnecessary; consider apalutamide dose reduction based on tolerability
ketoconazole[2]	23-38% increase in C_{max} and 28-51% increase in AUC of apalutamide	strong CYP 3A4 inhibition by ketoconazole	initial dose adjustment is unnecessary; consider apalutamide dose reduction based on tolerability
midazolam[2]	77% decrease in C_{max} and 92% decrease in AUC of midazolam	strong induction of CYP 3A4 by apalutamide	avoid concurrent use; if unavoidable, midazolam dose adjustment may be required
omeprazole[2]	77% decrease in C_{max} and 85% decrease in AUC of omeprazole	strong induction of CYP 2C19 by apalutamide	avoid concurrent use; if unavoidable, omeprazole dose adjustment may be required
rifampin[2]	15-25% decrease in C_{max} and 19-34% decrease in AUC of apalutamide	strong CYP 3A4 and moderate CYP 2C8 induction by rifampin	no dose adjustment necessary
rosuvastatin[2]	41% decrease in AUC of rosuvastatin	weak induction of BCRP and OATP1B1 by apalutamide	monitor for worsening lipid panel results; adjust rosuvastatin dose as required
warfarin[2]	16% decrease in Cmax and 46% decrease in AUC of S-warfarin	weak induction of CYP 2C9 by apalutamide	avoid concurrent use; if unavoidable, monitor INR; warfarin dose adjustment may be required

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Apalutamide_monograph.pdf

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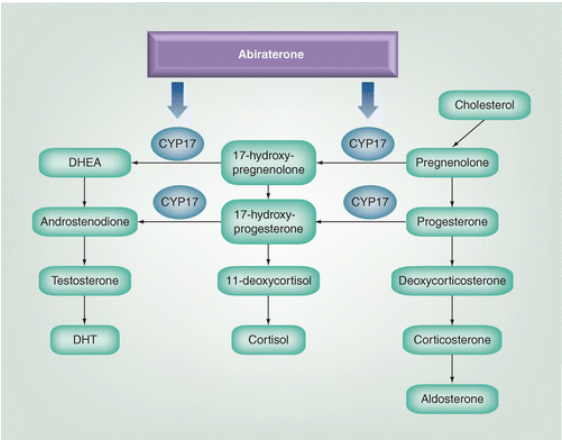
Apalutimide

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
TSH	Baseline and as clinically indicated
ECG	Baseline and as clinically indicated; more frequent in patients at risk of QTc increase
INR	If warfarin cannot be discontinued; baseline and during apalutamide treatment
Clinical toxicity assessment for androgen withdrawal effects, fatigue, infection, active cardiac disease, seizure, dermatologic toxicity and risk of fracture and falls	At each visit

https://www.cancercareontario.ca/en/drugformulary/drugs/apalutamide

Abiraterone



Abiraterone acetate: a promising drug for the treatment of castration-resistant prostate cancer Neeraj Agarwal, Thomas E Hutson, Nicholas J Vogelzang, and Guru Sonpavde Future Oncology 2010 6:5, 665-679

Abiraterone

- Abiraterone/Zytiga
- CYP17 Inhibitor
- 1000mg PO Daily + 5,g PO daily prednisone

PHARMACOKINETICS:

Oral Absorption	increased with food; time to peak plasma concentration 2 h	
Distribution	extensively distributed to peripheral tissues	
	cross blood brain barrier?	no information found
	volume of distribution	5630 L
	plasma protein binding	> 99%
Metabolism	abiraterone acetate rapidly converted to abiraterone in the liver	
	active metabolite(s)	abiraterone (primary)
	inactive metabolite(s)	abiraterone sulphate; N-oxide abiraterone sulphate
Excretion	primarily in feces	
	urine	5%
	feces	88%; abiraterone acetate (55%); abiraterone (22%)
	terminal half life	12 h
	clearance	no information found
Elderly	no clinically significant difference	

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Abiraterone_monograph.pdf

Abiraterone

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	angina (1-3%, severe <1%)
	arrhythmia (7%, severe 1%)
	cardiac failure (2%, severe 1-2%)
gastrointestinal	*emetogenic potential*: low[5]
	diarrhea (18-22%, severe <1%)
	dyspepsia (6-11%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	***peripheral edema*** (25%, severe 1%); see paragraph following **Side Effect** table
	fatigue (39%, severe 1%)[6]
infections and infestations	upper respiratory tract infection (5-13%)
	urinary tract infection (12%, severe 2%)
injury, poisoning, and procedural complications	fracture (6%, severe 1%)
investigations	ALT increase (11-41%, severe 1-6%); see paragraph following **Side Effect** table
	AST increase (30-36%, severe 2-3%); see paragraph following **Side Effect** table
	bilirubin increase (6-11%, severe <1%); see paragraph following **Side Effect** table
	cholesterol increase (55%, severe <1%)
	phosphorus decrease (23-26%, severe 5-7%)
	triglycerides increase (22-62%, severe <1%)
metabolism and nutrition	***hypokalemia*** (14-19%, severe 2-4%); see paragraph following **Side Effect** table
musculoskeletal and connective tissue	arthralgia[7] (27%, severe 4%)
	joint swelling, pain, or discomfort (31-32%, severe 2-5%)
	myopathy (36%, severe 5%)
renal and urinary	nocturia (6%)
	urinary frequency (7%, severe <1%)
	hematuria (10%, severe 1%)[8]
respiratory, thoracic and mediastinal	cough (11-17%)
skin and subcutaneous tissue	rash (8%)[9]
vascular	hot flush (19-23%, severe <1%)
	hypertension (9-22%, severe 1-4%); see paragraph following **Side Effect** table

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Abiraterone

- Fatigue

- Mineralocorticoid effects: ACTH increase
- →hypertension/hypokalemia/fluid retention
- →concomitant use of prednisone prevents

- Hepatotoxicity; usually w/in 3 months

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Abiraterone

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan[1,8]	AUC of dextromethorphan increased by 200%; AUC of active metabolite increased by 33%[6]	inhibition of CYP 2D6 metabolism of dextromethorphan and its metabolite, dextrorphan by abiraterone	consider therapy modification; monitor for toxicity related to dextromethorphan[9]
rifampicin[6]	AUC of abiraterone decreased by 55%[6]	strong induction of CYP 3A4 by rifampicin[6]	avoid concurrent therapy[6]

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Abiraterone

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure, serum potassium	Baseline and monthly
Liver function tests, bilirubin	Baseline, every 2 weeks for the first 3 months and monthly thereafter, or as clinically indicated
Monitor for adrenal insufficiency	As clinically indicated when prednisone is withdrawn, or during periods of infection/stress
Monitor for mineralocorticoid excess	As clinically indicated if patient continues on abiraterone after stopping prednisone
Cholesterol and triglycerides	Baseline, every 2 to 3 months and as clinically indicated
Clinical toxicity assessment for hypertension, edema, GI, musculoskeletal effects, hot flashes, urinary symptoms, cardiac and respiratory toxicity	At each visit

https://www.cancercareontario.ca/en/drugformulary/drugs/abiraterone

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