DRUG NAME: Niraparib-abiraterone

SYNONYM(S): MK4827 and CB7630[1], niraparib tosylate and abiraterone acetate[1]

COMMON TRADE NAME(S): AKEEGA®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Niraparib-abiraterone is an orally administered fixed-dose drug combination of niraparib and abiraterone. Niraparib is a poly (ADP-ribose) polymerase (PARP) enzyme inhibitor and targets PARP-1 and PARP-2. Binding to PARP inhibits single-stranded DNA base excision repair and creates PARP-DNA complexes that lead to double-stranded DNA breaks, ultimately causing cell death in tumours that cannot repair double-stranded breaks reliably. Niraparib has demonstrated anti tumour activity in tumour cell lines with or without mutations in BRCA 1/2. Niraparib is an immunosuppressive agent. Abiraterone selectively inhibits the CYP17 enzyme and reduces the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione. When used in addition to androgen deprivation therapies (luteinizing hormone releasing hormone [LHRH] agonists) or orchiectomy, abiraterone further decreases androgen production to below castrate levels.[2]

PHARMACOKINETICS:

Oral Absorption	niraparib: T_{max}= 3 h; abiraterone: T_{max}= 1.5 h; food increases absorption of abiraterone	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	niraparib: yes[3]; abiraterone: no[4]
	volume of distribution	niraparib: 1,117 L; abiraterone: 25,774 L
	plasma protein binding	niraparib: 83%; abiraterone: >99%
Metabolism	niraparib is metabolized by carboxylesterases; abiraterone acetate is rapidly converted to abiraterone in the liver where it is metabolized by CYP3A4 and SULT2A1	
	active metabolite(s)	niraparib: no information found abiraterone acetate: abiraterone
	inactive metabolite(s)	niraparib: M1 (major) and M10 abiraterone: N-oxide abiraterone sulphate and abiraterone sulphate
Excretion	niraparib: both hepatobiliary excretion and renal elimination; abiraterone: primarily by fecal elimination	
	urine	niraparib: 48%; abiraterone: 5%
	feces	niraparib: 39%; abiraterone: 88%
	terminal half life	niraparib: 62 h; abiraterone: 20 h
	clearance	niraparib: 16.7 L/h; abiraterone: 1673 L/h
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[2] unless specified otherwise.

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USES:

Primary uses:

*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- patients with ***pre-existing cardiovascular disease*** may experience worsening ***hypertension***, ***hypokalemia*** and ***fluid retention***; optimize cardiac function and correct hypokalemia prior to initiating treatment[2]
- ensure pre-existing ***hypertension*** is adequately controlled prior to starting treatment[2]
- niraparib-abiraterone in combination with ***radium 223 dichloride*** is not recommended due to the increased risk of fracture and mortality; radium 223 dichloride treatment should not be initiated for at least 5 days after the last dose of niraparib-abiraterone[5]
- ***myelodysplastic syndrome/acute myeloid leukemia*** (MDS/AML) have been reported in patients who have received niraparib[2]

Carcinogenicity: Carcinogenicity studies have not been conducted with niraparib. Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) has been reported in patients who have received niraparib as monotherapy and in combination.[5] In animal studies, abiraterone was not carcinogenic in mice or female rats. However, an increased incidence of interstitial cell neoplasms in the testes was reported in male rats. Clinical significance is unknown as this finding in male rats is considered related to the pharmacological action of abiraterone and specific to rats.[2]

Mutagenicity: Niraparib was not mutagenic in Ames test, but it was clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. Abiraterone was not mutagenic in Ames test and not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies with niraparib, reduced spermatogenesis, small testes, and germ cell depletion (in the testes and epididymides) were observed at exposures lower than those seen following human clinical exposure. The changes were largely reversible within 4 weeks after the last dose.[2,3] In animal studies, abiraterone reduced fertility in both male and female rats.[6]The changes were completely reversible 4-16 weeks after abiraterone was stopped. Reduced sperm counts/motility and altered sperm morphology were also reported in male test subjects. Untreated female test subjects mated with treated males showed reduced number of corpora lutea, implantations, and live embryos, as well as increased pre-implantation loss. Treated female rats showed an increased incidence of irregular or extended estrous cycles and pre-implantation loss.[2]

Pregnancy: Reproductive studies with niraparib have not been conducted. However, based on its mechanism of action, niraparib may cause fetal harm if used during pregnancy. Niraparib is genotoxic and actively targets dividing cells; therefore, it has the potential to cause teratogenicity and embryo-fetal death. In animal studies, oral administration of abiraterone to pregnant rats during organogenesis caused developmental toxicity at exposures lower than those seen following human clinical exposure. Findings included embryo-fetal lethality, fetal developmental delay, urogenital effects, and decreased fetal weight. It is not known if niraparib, abiraterone, or their metabolites are present in semen. It is recommended that male patients taking niraparib-abiraterone use a condom during sexual activity with a pregnant woman OR a condom plus a second contraceptive method during sexual activity with a woman of childbearing potential for the duration of treatment and for at least 3 months after the last dose. The safety and efficacy of niraparib-abiraterone in females have not been established.[2]

Breastfeeding is not recommended due to potential secretion into breast milk.[5]

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SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (46%, severe 30%)
	leukopenia (10%, severe 2%)
	lymphopenia (9%, severe 4%)
	neutropenia (14%, severe 7%)
	thrombocytopenia (21%, severe 7%)
cardiac (see paragraph following **Side Effects** table)	***arrhythmia*** (13%, severe 1%)
	heart failure (2%)
	ischemic heart disease (2%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal distention (4%)
	abdominal pain (5%)
	constipation (31%)
	diarrhea (17-20%, severe <1%)
	dry mouth (10%, severe <1%)
	dyspepsia (6%)
	nausea (24%, severe <1%)
	vomiting (13%, severe <1%)
general disorders and administration site conditions	asthenia (16%, severe <1%)
	peripheral edema (17%)[5,10]; see paragraph following **Side Effects** table
	fall (10%, severe 1%)[5]
	fatigue (26%, severe 3%)
immune	anaphylaxis[2]
infections and infestations	conjunctivitis (<1%)
	urinary tract infection (9%, severe 3%)
	urosepsis (<1%)
injury, poisoning, and procedural complications	fracture (<10%)[10]
investigations	alkaline phosphatase increase (10-34%, severe 2-5%)[2,5]
	ALT increase (18%, severe 1%)[5]; see paragraph following **Side Effects** table
	AST increase (20%, severe 2%)[5]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	blood bilirubin increase (12%)[5]
	creatinine increase (9-30%, severe 1%)[2,5]
	gamma-glutamyl transferase increase (<1%)
	QTc prolongation (<1%)
	weight loss (9%, severe 1%)
metabolism and nutrition	appetite decrease (14%, severe <1%)
	hyperkalemia (25%, severe 3%)
	hypokalemia (14%, severe 4%); see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (13%, severe <1%)
	musculoskeletal pain (44%, severe 4%)[5]
nervous system	dizziness (11%, severe <1%)
	headache (12%, severe 1%)[5]
psychiatric	insomnia (10%)
renal and urinary	acute kidney injury (3%)[5]
	hematuria (7%, severe <1%)
	dysuria (5%)
respiratory, thoracic, and mediastinal	COVID-19 infection (13%, severe 7%)
	cough (7%)
	dyspnea (16%, severe 2%)
	pneumonitis (2%)
skin and subcutaneous tissue	photosensitivity (<1%)
	rash (7%)
vascular	hemorrhage (12%, severe 2%)[5]
	hot flashes[6,11]
	hypertension (31%, severe 15%); see paragraph following **Side Effects** table
	thromboembolism (8%, severe 5%); includes pulmonary embolism, cerebrovascular accident[5], deep vein thrombosis

Adapted from standard reference[2] unless specified otherwise.

Hematologic toxicities (anemia, neutropenia, thrombocytopenia) are reported with niraparib-abiraterone, including grade 3 and 4 events. Most events occur during the first two months of treatment. Complete blood counts should be monitored before and throughout the treatment. Management of hematologic toxicity may include treatment interruption, dose reduction, and/or transfusion. Permanently discontinue niraparib-abiraterone if severe hematologic toxicity does not resolve within four weeks of treatment interruption.[2]

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including fatal cases, have been reported in patients receiving niraparib as monotherapy and in combination. Possible risk factors for MDS/AML include previous radiotherapy, platinum chemotherapy and/or other DNA damaging agents.[3] For suspected MDS/AML or prolonged

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hematological toxicities, referral to hematologist is recommended. Permanently discontinue niraparib-abiraterone if MDS/AML is confirmed.[2]

Abiraterone causes a compensatory ACTH-mediated ***mineralocorticoid excess***. The mineralocorticoid effects can lead to ***hypertension, hypokalemia,*** and ***fluid retention***, potentially worsening pre-existing cardiovascular disease. Niraparib can independently cause ***hypertension***. The median time to onset of hypertension in patients treated with niraparib-abiraterone is 56 days. ***QTc prolongation*** has been reported in patients experiencing hypokalemia during treatment with niraparib-abiraterone. Blood pressure should be adequately controlled and hypokalemia corrected prior to starting treatment with niraparib-abiraterone. For patients with heart failure, cardiac function should be optimized before initiating treatment. Additional monitoring may be indicated in patients with history of cardiovascular disease (e.g., myocardial infarction, thrombosis, unstable angina or arrythmia). Concomitant use of corticosteroids during treatment with niraparib-abiraterone suppresses ACTH drive which reduces the incidence and severity of mineralocorticoid effects. If corticosteroids are withdrawn, monitor for adrenocortical insufficiency. If niraparib-abiraterone is continued after corticosteroids are withdrawn, monitor for symptoms of mineralocorticoid excess. Avoid choosing spironolactone as a potassium-sparing diuretic because it may stimulate the androgen receptor and cause disease progression.[2]

Severe ***hepatotoxicity*** with marked increases in liver enzymes has been reported with niraparib-abiraterone. Abiraterone monotherapy has been associated with serious hepatotoxicity such as fulminant hepatitis and active liver failure, including fatal cases.[5] Regular monitoring of serum transaminases and bilirubin during treatment is recommended. Management of hepatotoxicity may include treatment interruption and dose reduction. If hepatotoxicity recurs at the reduced dose of niraparib-abiraterone, permanently discontinue treatment.[2]

Posterior Reversible Encephalopathy Syndrome (PRES) has been reported in patients receiving niraparib monotherapy.[10] Symptoms of PRES may include seizures, headache, altered mental status, visual disturbance, and cortical blindness. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. If PRES is confirmed during treatment, permanently discontinue niraparib-abiraterone.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan[2]	AUC of dextromethorphan increased by 200%; AUC of active metabolite increased by 33%	inhibition of CYP 2D6 by abiraterone	consider dextromethorphan dose reduction and monitor for toxicity
ketoconazole[2]	no clinically meaningful effect on the pharmacokinetics of abiraterone	strong inhibition of CYP 3A4 by ketoconazole	no dose adjustment is required
pioglitazone[2]	AUC of pioglitazone increased by 46%; severe hypoglycemia has been reported	inhibition of CYP 2C8 by abiraterone	monitor for hypoglycemia; pioglitazone dose reduction may be required
repaglinide[5]	severe hypoglycemia has been reported	inhibition of CYP 2C8 by abiraterone	monitor for hypoglycemia; repaglinide dose reduction may be required
rifampicin[2]	AUC of abiraterone decreased by 55%	strong induction of CYP 3A4 by rifampicin	avoid concurrent therapy

No formal drug interaction studies have been performed with niraparib. Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs).[2] *In vitro*, niraparib weakly induces CYP 1A2 and inhibits MATE-1 and -2 and BCRP, P-gp and OCT1; clinical significance is unknown.[2]

Abiraterone is a substrate of ***CYP 3A4***. Strong ***inducers*** of CYP 3A4 may decrease the plasma concentration of abiraterone; avoid concurrent therapy.[2] Abiraterone is an ***inhibitor*** of ***CYP 2D6 and CYP 2C8.*** Avoid concurrent use with CYP 2D6 or CYP 2C8 substrates that have narrow therapeutic index; if unavoidable, consider dose reduction of the substrate and monitor for toxicity.

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In vitro, abiraterone is an inhibitor CYP 2C9, CYP 2C19 and CYP 3A4/5 and a substrate of OATP1B1; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Janssen Inc. supplies niraparib-abiraterone as a film-coated tablet in two strengths, one containing 100 mg niraparib and 500 mg abiraterone per tablet (regular strength) and the other containing 50 mg niraparib and 500 mg abiraterone per tablet (low strength). Tablets contain lactose. Store at room temperature.[2,12]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[2,13,14]*:*	***niraparib 200 mg and abiraterone 1000 mg*** (2 regular strength tablets) ***PO once daily*** (range niraparib 100-200 mg and abiraterone 500-1000 mg per day) Administer on an empty stomach (one hour before or two hours after food).[2]
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	creatinine clearance ≥30 mL/min: no adjustment required[2] creatinine clearance <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure[2,10]*:*	mild impairment (Child-Pugh Class A or AST/ALT ≤3xULN or bilirubin ≤1.5xULN): no adjustment required moderate to severe impairment (Child-Pugh Class B and C): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy not established

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