DRUG NAME: Nilutamide

SYNONYM(S):

COMMON TRADE NAME(S): ANANDRON®

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Nilutamide is a nonsteroidal antiandrogen which competitively inhibits the binding of androgens to the androgen receptor.[1] It is devoid of other endocrine activity. Nilutamide is structurally and pharmacologically related to bicalutamide and flutamide.

Prostate cancer is a mostly androgen-dependent cancer and can be treated with surgical or medical castration. Luteinizing hormone releasing hormone agonists (LHRHa) suppress pituitary release of luteinizing hormone (LH) and result in medical castration. Unlike medical castration, nonsteroidal antiandrogens do not decrease the production of androgens. The initial stimulation of the pituitary caused by LHRHa produces an acute increase in the concentration of plasma testosterone accompanied by temporary worsening of symptoms (flare reaction). To avoid the flare reaction, antiandrogens should be given concurrently with the first administration of LHRHa.

Antiandrogens are also used in combination with LHRHa to inhibit the effects of testicular and adrenal androgens (maximum androgen blockade). In some patients with metastatic prostate cancer (15-20%),[2] antiandrogen withdrawal may lead to a paradoxical decrease in serum prostate-specific antigen level (antiandrogen withdrawal syndrome).[1]

PHARMACOKINETICS:

Oral Absorption	rapid and complete	
Distribution	steady-state achieved within 14 days	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	84%
Metabolism	hepatic, involves the hepatic microsomal enzyme oxidation system	
	active metabolite	hydroxymethylnitro derivative
	inactive metabolite(s) [3]	hydroxylated derivatives and secondary alcohols
Excretion	urine [3,4]	≤78%, <1-3% unchanged
	feces	1-7%
	terminal half life	56 h (range 23-87 h)
	clearance	no information found

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients with the following conditions[1]:
- a history of hypersensitivity reaction to nilutamide
- severe respiratory insufficiency
- severe hepatic impairment or serum transaminase levels >2-3 times the upper limit of normal[1,5]

Caution:
- **Disulfiram-like reaction:** Patients receiving nilutamide should be informed about the risk of a disulfiram-like reaction, characterized primarily by rash and hot flashes,[3] if alcohol is consumed[1]; if this reaction occurs, alcohol should be avoided.[4]
- **Vision changes:** Patients receiving nilutamide should be advised regarding vision changes with nilutamide specifically the increase in light adaptation time when passing from a well lit area to a dimly lit area[1]; see paragraph following the **Side Effects** table.

Special populations:
- Patients of ***Japanese origin*** may be at increased risk for developing interstitial pneumonitis (13-17%) with nilutamide.[1,5] These patients may also have a higher incidence of elevated serum transaminase levels (19%).[1] Use nilutamide with caution when treating Asian patients[1]; see paragraph following the **Side Effects** table.
- Because of its intended use, safety and efficacy have not been established in ***women*** and ***children***. Nilutamide is indicated only for use in male patients.[1]

Carcinogenicity: Animal studies show carcinogenic potential when used as monotherapy. This effect is attributable to elevated LH concentrations resulting from loss of feedback inhibition, which does not occur with medical and surgical castration.[6]

Mutagenicity: Nilutamide is not mutagenic in Ames test and mammalian *in vitro* mutation test. Nilutamide is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: Animal studies show no effect on reproductive function at doses equivalent to 1-2 times the human dose.[7]

Pregnancy: FDA Pregnancy Category C.[4] Animal studies have shown fetal risks and there are no controlled studies in women *or* studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk; because of its intended use, safety and efficacy have not been established in women.[1]

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.[8] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** **Side effects and incidence are those of nilutamide when used with surgical or medical castration unless otherwise specified.**	
blood/bone marrow/ febrile neutropenia	anemia (<1%), aplastic anemia (<1%); fatalities have occurred, causality not established
	neutropenia[3,9] (<1%)[3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** **Side effects and incidence are those of nilutamide when used with surgical or medical castration unless otherwise specified.**	
cardiovascular (arrhythmia)	tachycardia or palpitations (<1%)
cardiovascular (general)	angina (<1%)
constitutional symptoms	increased appetite, weight gain (<1%)
	insomnia[4]
	fatigue[10]
dermatology/skin	maculopapular rash (<1%)
	pruritis[3] (<5%),[3,10] urticaria (<1%)
endocrine	gynecomastia (4-11%), monotherapy (44%); reversible
	hot flashes (14-67%)[3,4]
gastrointestinal	*emetogenic potential: rare*[11]
	abdominal cramps[3,10]
	nausea (4-25%),[3] monotherapy (32%)[3,10]; typically mild[3,4]
	vomiting (<1%)
hepatobiliary/pancreas	hepatic dysfunction (1%)[4,5]; see paragraph following the **Side Effects** table
lymphatics	edema (2%)
metabolic/laboratory	elevated serum transaminases (1-13%),[3,4,10] monotherapy[3] (2%)[3]; see paragraph following the **Side Effects** table
musculoskeletal	cold extremities (<1%)
neurology	CNS reactions including: dizziness (3%), depression (1%), insomnia (1%), anxiety (<1%), drowsiness (<1%)
ocular/visual	***visual disturbances***; see paragraph following the **Side Effects** table
pain	headache (<1%)
pulmonary	dyspnea (1%)
	interstitial pneumonitis (1-2%)[1,3,4]; see paragraph following the **Side Effects** table
sexual/reproductive function	loss of libido, impotence (≤100%),[3] monotherapy (52%)[3,10]
	testicular atrophy[4] (16%)[4]
syndromes	alcohol-intolerance syndrome (disulfiram-like reaction) (4-5%)[4]
vascular	cerebrovascular ischemia (<1%)

Adapted from standard reference[1] unless specified otherwise.

Reversible visual disturbances including delays in adapting to changes in light to dark (13-90%) may occur with nilutamide use.[1,4,5] These delays may last anywhere from seconds to a few minutes.[4,5] Patients receiving nilutamide should be cautioned about driving at night or through tunnels should this occur.[1,4,5] Ophthalmic examination reveals an increase in the photostress recovery time in these patients.[3] Impaired adaptation to darkness may be minimized by wearing tinted glasses when exposed to bright light.[1,4,5] The effect generally persists with ongoing therapy but may resolve with a dose reduction[4,5]; however, 1-2% of patients will require discontinuation of nilutamide.[4,10] Chromatopsia (3-9%),[1,4] photophobia (1%),[1] and blurred vision (<1%)[1] have also been reported with nilutamide use.

Interstitial pneumonitis has occurred in 1-2% of patients receiving nilutamide.[1,3,4] Pneumonitis typically resolves following cessation of therapy; however, fatalities have occurred. A higher incidence of pneumonitis (13-17%)[1,5] has been reported in patients of Japanese origin. Symptoms include progressive exertional dyspnea, cough, chest pain, and fever which may occur during the first 3 months of therapy. [4,5] Nilutamide therapy should be discontinued at the onset of symptoms and consideration given to starting corticosteroid treatment.[1] A dose reduction of 50% has enabled continuation of therapy in patients with mild pneumonitis.[3] Rechallenge has resulted in recurrence of symptoms.[3]

Hepatic dysfunction (1%)[4,5] including elevated serum transaminase levels, jaundice, hepatocellular or mixed liver injury, hepatitis, and death have been reported with nilutamide.[1,5] Patients of Japanese origin may have a higher incidence of elevated serum transaminases levels (19%).[1] Hepatic toxicities typically occur within the first 3-4 months of treatment.[5] Appropriate liver function tests should be measured at regular intervals during the first 4 months of therapy.[5] Liver function tests should also be obtained at the first signs and symptoms suggestive of liver dysfunction; e.g., nausea, vomiting, abdominal pain, lack of appetite, pruritis, fatigue, dark urine, persistent anorexia, unexplained "flu-like" symptoms, hyperbilirubinuria, jaundice, or right upper quadrant tenderness.[5] If at any time a patient has jaundice, or transaminase levels rise > 2-3 times the upper limit of normal, nilutamide should be immediately discontinued with close follow-up of liver function tests until resolution.[1,5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
alcohol[1]	possible disulfiram-like reaction (4-5%)[4]	unknown	caution

Nilutamide is a major CYP2C19 substrate; therefore, drugs or herbs that are CYP2C19 inducers may decrease the levels/effects of nilutamide. Likewise, drugs or herbs that are CYP2C19 inhibitors may increase the levels/effects of nilutamide.[4,12]

Nilutamide is a weak CYP2C19 inhibitor.[4] *In vitro* nilutamide inhibits the activity of certain hepatic cytochrome P450 isoenzymes and may therefore increase the levels/effect of agents requiring these systems. [1,13] When nilutamide is administered with drugs with a low therapeutic margin (e.g., warfarin, phenytoin, theophylline) additional monitoring may be required.[1,13]

SUPPLY AND STORAGE:

Tablets: sanofi-aventis Canada supplies nilutamide as a 50 mg tablet. Selected non-medicinal ingredients: lactose. Store at room temperature, protect from light and excessive moisture.[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral:

initial dose: 300 mg PO once daily for ≤30 days[1]
maintenance dose: 150 mg (range 150-300 mg)[3] ***PO once daily[1,14,15]***

- administer with food or on an empty stomach[4,5]; the manufacturer recommends administering nilutamide before breakfast

Concurrent radiation:

no dose adjustment required[8]

BCCA usual dose noted in ***bold, italics***

Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no adjustment required[3]
Dosage in hepatic failure:	extensive hepatic metabolism[1,3]; not recommended in patients who develop jaundice or with serum transaminase levels >2-3 times the upper limit of normal[1,5]
Dosage in dialysis:	no information found

Children:

no information found regarding the use of nilutamide in pediatric oncology

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