Drug Monograph

A - Drug Name

niLUTAmide

SYNONYM(S): RU-23908

COMMON TRADE NAME(S): Anandron® ()

back to top

B - Mechanism of Action and Pharmacokinetics

Nilutamide is a pure, specific nonsteroidal anti-androgen which blocks androgen binding to androgen receptors

Absorption	Oral absorption: Yes, rapidly and completely	
Distribution	Pharmacokinetics are dose-related. Steady state achieved after two weeks.	
	Cross blood brain barrier?	no information found
	PPB	84 %
Metabolism	Liver, involves hepatic microsomal enzyme oxidation system.	
	Active metabolites	hydroxymethylnitro derivative.
	Inactive metabolites	yes
Elimination	Mainly in urine as metabolites; 1.4 - 7% in feces within 4-5 days.	

Urine	62%, 3% unchanged
Half-life	56 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Metastatic prostate cancer (stage D2, in conjunction with surgical castration)

back to top

D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Not applicable

The following adverse effects were reported in placebo-controlled clinical trials in conjunction with surgical/medical castration. Severe adverse effects from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Angina (2%)	E
	Heart failure (1%)	E
	Hypertension (1%)	E
	Palpitations , tachycardia (rare)	E
	QT interval prolonged (with combined androgen blockade, rare)	E D
	Thromboembolism (1%) (stroke)	E
Dermatological	Hirsutism (rare)	E
	Pruritus (1%)	I E
	Rash (rare)	I E
Gastrointestinal	Anorexia (1%)	E

	Constipation (3%)	E
	Diarrhea (rare)	E
	Dry mouth (rare)	E
	Gastrointestinal pain (1%)	E
	Nausea, vomiting (4%)	I E
General	Edema (2%)	E
	Fatigue (1%)	E
	Other (4%) (alcohol intolerance)	I
Hematological	Anemia (1%)	E D
	Bone marrow hypocellular (aplastic anemia - very rare)	E D
Hepatobiliary	Hepatic failure (<1%)	D
	↕ LFTs (2%)	E
Metabolic / Endocrine	Hyperglycemia (1%)	E
Musculoskeletal	Other - Bone loss (rare, after long-term use)	L
Nervous System	Anxiety (rare)	E
	Depression (1%)	E
	Dizziness (3%)	E
	Headache (3%)	E
	Sleep disorder (1%)	E
Ophthalmic	Eye disorders (11%) (retarded light-to-dark adaptation)	E
	Other (3%) (visual disturbances)	E
	Photophobia (1%)	E
Reproductive and breast disorders	Erectile dysfunction (1%)	E
	Gynecomastia (1%)	E
Respiratory	Dyspnea (1%)	E
	Pneumonitis / Interstitial Lung Disease (1%)	D
Vascular	Hot flashes (14%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)

D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for niLUTAmide include hot flashes, eye disorders, nausea, vomiting, constipation, dizziness, headache, other, ↑ lfts and edema.

Retarded light-to-dark adaptation usually improves on treatment, and usually resolves when treatment is discontinued. Patients should be cautioned about driving at night or through tunnels. This effect can be alleviated by wearing tinted glasses.

Bone loss may occur during the hypoandrogenic state caused by long-term use of nilutamide. Risk factors such as older age, pre-existing osteopenia, family history of osteoporosis, chronic use of corticosteroids, anticonvulsants, or other drugs that may lead to osteoporosis or chronic alcohol/tobacco abuse should be carefully considered before starting treatment.

Androgen deprivation may increase cardiovascular risk (MI, sudden death, stroke) in men with prostate cancer since it can adversely affect cardiovascular risk factors, such as increased body weight, reduced insulin sensitivity and/or dyslipidemia.

QTc prolongation has been described with combined androgen blockade and nilutamide should be used with caution in patients with other risk factors such as congenital long QT syndrome, abnormal electrolytes and concomitant medications which prolong QTc.

Reduction in glucose tolerance and increased risk of developing diabetes have been reported in men treated with androgen deprivation therapy. Anemia is also a known physiologic effect of testosterone suppression.

Interstitial pneumonitis has been described, with an apparently higher incidence in patients of Japanese origin (13%). It generally occurs within the first 3 months of therapy, and may resolve after treatment discontinuation or lead to death in some cases. Interrupt nilutamide treatment if new or worsening dyspnea or other signs of pneumonitis occur. Treatment should be discontinued if pneumonitis is diagnosed, and the use of steroids should be considered. Patients of Japanese origin may also be at a high risk of **liver function test abnormalities** (19%). Hepatotoxicity generally occurs 3-4 months after starting nilutamide, and results in drug discontinuation in 1% of patients.

Antiandrogen withdrawal syndrome has been described; after discontinuation for disease progression, 6-8 weeks should elapse before making further treatment decisions.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Oral:

- Initial: 300mg daily for 30 days*, then
- Maintenance: 150mg once daily

(* may start maintenance earlier should intolerance occur)

Dosage with Toxicity:

Toxicity	Dose Adjustment
Myelosuppression	No adjustment required
Suspected pneumonitis	Hold, investigate and treat appropriately; discontinue if confirmed
QT prolongation	Discontinue

Dosage with Hepatic Impairment:

If transaminases >2-3x upper limit of normal, interrupt treatment and monitor liver function closely. Discontinue if severe hepatic impairment.

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

No adjustment required.

Dosage based on ethnicity:

A higher rate of interstitial pneumonitis and elevated transaminases were reported in Japanese patients. Use with caution when treating Asian patients.

Children:

Contraindicated

back to top

F - Administration Guidelines

- Take tablet(s) by mouth, before breakfast.
- Avoid alcoholic beverages during treatment.
- If a dose is missed, the next dose should be taken at the usual time. A double dose should not be taken to make up for missed doses.
- Store between 15 to 30°C.

back to top

G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to the drug or to any constituents of the drug product.
- Patients with severe hepatic dysfunction or with severe respiratory insufficiency.
- Nilutamide is contraindicated in women and children.
- Contains lactose; should not be used in patients with hereditary galactose/glucose/lactase disorders.

Other Warnings/Precautions:

- Patients taking nilutamide should be warned against consuming alcohol because of a possible disulfiram-like reaction.
- Patients should be advised regarding impairment of light adaptation if they plan to operate a vehicle or machinery.
- Nilutamide should not be administered to patients with congenital long QT syndrome, and should be discontinued in patients who develop QT prolongation.

Pregnancy and Lactation:

- Fertility effects: Probable
  - Nilutamide should not be used by women. In the laboratory, this drug may harm or affect the embryos or offspring of animals exposed to it.
  - If there is a chance of pregnancy in a female partner, adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (general recommendation)

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Alcohol	Possible disulfiram-like reaction (4%)	Unknown	Avoid
Drugs metabolized by hepatic microsomal enzymes (e.g., warfarin, phenytoin, propranolol, chlordiazepoxide, lidocaine, diazepam, theophylline)	Possible ↑ in serum levels of these drugs if given with nilutamide	Inhibition of CYP2C19 by nilutamide	Monitor for increased pharmacological effect/toxicity with drugs that have a narrow therapeutic index; adjust doses as required
Drugs that increase QT interval	↑ risk of QT prolongation or Torsades de pointes	Additive	Caution; monitor closely

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and as clinically indicated
Blood glucose levels/HbA1c	Baseline and at each visit, especially in diabetic patients
EKG, Electrolytes (including K, Ca, Mg)	Baseline, and regularly for at risk patients
Chest X-ray +/- pulmonary function tests	Baseline and as clinically indicated
Clinical toxicity assessment for androgen deprivation symptoms, ocular and respiratory effects, and cardiovascular effects.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
INR for patients on warfarin	Baseline and as clinically indicated

back to top

J - Supplementary Public Funding

ODB - General Benefit (
ODB Formulary
)

- niLUTAmide ()

back to top

K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA).

Nilutamide: e-Drugdex, Micromedex Healthcare Series.

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1188-9.

Product Monograph: Anandron® (nilutamide). Sanofi-aventis Canada Inc., June 13, 2016.

Nilutamide. Lexi-Drugs Online. Lexicomp Inc. Updated July 13, 2018.

September 2018 Updated adverse effects, monitoring and administration

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top