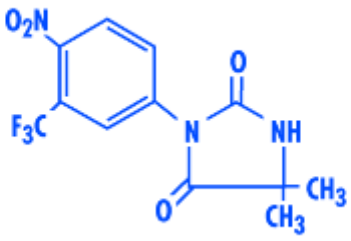
NILANDRON® Prescribing Information
(nilutamide) Tablets

Rx only

DESCRIPTION

NILANDRON® tablets contain nilutamide, a nonsteroidal, orally active antiandrogen having the chemical name 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione with the following structural formula:



Nilutamide is a microcrystalline, white to practically white powder with a molecular weight of 317.25. Its molecular formula is $C_{12}H_{10}F_3N_3O_4$.

It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [< 0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

Each NILANDRON tablet contains 150 mg of nilutamide. Other ingredients in NILANDRON tablets are corn starch, lactose, povidone, docusate sodium, magnesium stearate, and talc.

BACK TO TOP

CLINICAL PHARMACOLOGY

Mechanism of Action

Prostate cancer is known to be androgen sensitive and responds to androgen ablation. In animal studies, nilutamide has demonstrated antiandrogenic activity without other hormonal (estrogen, progesterone, mineralocorticoid, and glucocorticoid) effects. In vitro, nilutamide blocks the effects of testosterone at the androgen receptor level. In vivo, nilutamide interacts with the androgen receptor and prevents the normal androgenic response.

Pharmacokinetics

Absorption:

Analysis of blood, urine, and feces samples following a single oral 150-mg dose of [^{14}C]-nilutamide in patients with metastatic prostate cancer showed that the drug is rapidly and completely absorbed and that it yields high and persistent plasma concentrations.

Distribution:

After absorption of the drug, there is a detectable distribution phase. There is moderate binding of the drug to plasma proteins and low binding to erythrocytes. The binding is nonsaturable except in the case of alpha-1-glycoprotein, which makes a minor contribution to the total concentration of proteins in the plasma. The results of binding studies do not indicate any

effects that would cause nonlinear pharmacokinetics.

Metabolism:

The results of a human metabolism study using ^{14}C-radiolabelled tablets show that nilutamide is extensively metabolized and less than 2% of the drug is excreted unchanged in urine after 5 days. Five metabolites have been isolated from human urine. Two metabolites display an asymmetric center, due to oxidation of a methyl group, resulting in the formation of D- and L-isomers. One of the metabolites was shown, in vitro, to possess 25 to 50% of the pharmacological activity of the parent drug, and the D-isomer of the active metabolite showed equal or greater potency compared to the L-isomer. However, the pharmacokinetics and the pharmacodynamics of the metabolites have not been fully investigated.

Elimination:

The majority (62%) of orally administered [^{14}C]-nilutamide is eliminated in the urine during the first 120 hours after a single 150-mg dose. Fecal elimination is negligible, ranging from 1.4% to 7% of the dose after 4 to 5 days. Excretion of radioactivity in urine likely continues beyond 5 days. The mean elimination half-life of nilutamide determined in studies in which subjects received a single dose of 100-300 mg ranged from 38.0 to 59.1 hours with most values between 41 and 49 hours. The elimination of at least one metabolite is generally longer than that of unchanged nilutamide (59-126 hours). During multiple dosing of 150 mg nilutamide (given as 3 x 50 mg) twice a day, steady state was reached within 2 to 4 weeks for most patients, and mean steady state AUC_{0-12} was 110% higher than the $AUC_{0-\infty}$ obtained from the first 150 mg dose. These data and in vitro metabolism data suggest that, upon multiple dosing, metabolic enzyme inhibition may occur for this drug.

Clinical Studies

Nilutamide through its antiandrogenic activity can complement surgical castration, which suppresses only testicular androgens. The effects of the combined therapy were studied in patients with previously untreated metastatic prostate cancer.

In a double-blind, randomized, multicenter study that enrolled 457 patients (225 treated with orchiectomy and NILANDRON, 232 treated with orchiectomy and placebo), the NILANDRON group showed a statistically significant benefit in time to progression and time to death. The results are summarized below.

	NILANDRON	PLACEBO
Median Survival (months)	27.3	23.6
Progression-Free Survival (months)	21.1	14.9
Complete or Partial Regression	41%	24%
Improvement in Bone Pain	54%	37%

BACK TO TOP

INDICATIONS AND USAGE

Metastatic Prostate Cancer

NILANDRON tablets are indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

For maximum benefit, NILANDRON treatment must begin on the same day as or on the day after surgical castration.

BACK TO TOP

CONTRAINDICATIONS

NILANDRON tablets are contraindicated:

- in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment)
- in patients with severe respiratory insufficiency
- in patients with hypersensitivity to nilutamide or any component of this preparation.