DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Daisy Chhatwal
US Drug Regulatory Affairs & Compliance
Aventis Pharmaceuticals, Inc.
399 Interpace Parkway
Parsippany, NJ 07054

RE: Nilandron® (nilutamide) Tablets
NDA 20-169
MACMIS ID#9904

Dear Ms Chhatwal:

This letter concerns several promotional materials (sales aid 50060164/20199901/4286T0, wholesaler fact sheet 21017301/0230A1, and web sites www.aventispharma-us.com/our_products.htm and www.aventispharma-us.com/presskits/nilandron/overview_TXT.html) for Nilandron (nilutamide) tablets disseminated by Aventis Pharmaceuticals, Inc. (Aventis). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and has concluded that they are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. A description of our objections follows.

Use of Outdated Product Labeling

The web site www.aventispharma-us.com/our_products.htm is violative because it links to an outdated version of the approved product labeling (PI) for Nilandron that lacks serious risk information about the product. The failure to provide the current PI results in the omission of important safety information as described below.

The Food and Drug Administration (FDA) approved revisions to the Nilandron PI on September 29, 2000. These revisions included adding risk information in a Boxed Warning and other warnings regarding hospitalization and death due to both interstitial pneumonitis and severe liver injury in patients treated with Nilandron. Additionally, a warning that Nilandron is not indicated in women and should not be used in this population was included in the revised PI. Although your web page states that the Aventis web site was updated on April 6, 2001, the "Nilandron Prescribing Information" is linked to a September 1996 version of the PI. Your failure to provide the most current PI misbrands Nilandron. DDMAC is especially concerned with this violation since your omission of information concerning these potentially fatal risks associated with Nilandron treatment raises significant safety concerns.

Lack of Fair Balance

Your sales aid, wholesaler fact sheet, and web site www.aventispharma-us.com/presskits/nilandron/overview_TXT.html include claims such as, "Well-tolerated one tablet once a day therapy for patients with advanced prostate cancer," "Favorable side effect profile," and "Nilandron is generally well tolerated....." These claims are misleading because they minimize the potentially fatal adverse reactions associated with Nilandron, such as hospitalization and death due to interstitial pneumonitis and severe liver injury. Additionally, your web site states that "Interstitial pneumonitis has been reported in 2% of Nilandron patients." However, you fail to mention that in a small study, 17% of Nilandron patients developed interstitial pneumonitis according to the Boxed Warning in the PI.

The statement in your sales aid, "Visual disturbances are generally mild and tend to disappear spontaneously or after planned dosage reduction" is misleading because it minimizes the risk of visual disturbances and is inconsistent with the bolded warning in the PI. The PI states "In clinical trials, 13% to 57% of patients receiving Nilandron reported a delay in adaptation to dark, ranging from seconds to a few minutes, when passing from a lighted area to a dark area. This effect sometimes does not abate as drug treatment is continued." Furthermore, the PI also states "Patients who experience this effect should be cautioned about driving at night or through tunnels."

In addition, promotional materials are lacking in fair balance if they fail to present information relating to side effects and warnings with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. Your sales aid is misleading because of the inadequate prominence provided to Nilandron's risk information. For example, the Boxed Warning and other warnings are presented in single-spaced paragraph format, whereas the efficacy claims appear as bolded and bulleted statements that are presented in conjunction with large colorful charts and graphs.

Requested Action

Aventis should immediately discontinue these and all other promotional materials for Nilandron that contain the same or similar claims or presentations. We request that Aventis respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than April 24, 2001. This response should list all similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9904 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

/s/

Barbara Chong
4/10/01 10:06:26 AM

Well-tolerated one tablet once a with advanced prostate cancer[5*]

Favorable side effect profile

- Low incidence of diarrhea (≤2%)
- Low incidence of breast tenderness (≤2%)

Most frequently reported adverse events (greater than 5%) during a multicenter clinical trial comparing Nilandron + orchiectomy (n=225) to placebo + orchiectomy (n=232).

Initial dose 300 mg/day; maintenance dose 150 mg/day.

Percentage of all adverse experiences[4]

Adverse Experience	Nilandron + Orchiectomy (n=225)	Placebo + Orchiectomy (n=232)
Hot flushes	28.4	22.4
Impaired adaptation to dark	12.9	1.3
Nausea	9.8	6.0
Urinary tract infection	8.0	9.1
Increased AST	8.0	3.9
Increased ALT	7.6	4.3
Constipation	7.1	3.9
Dizziness	7.1	3.4
Abnormal vision	6.7	1.7
Dyspnea	6.2	7.3
Hypertension	5.3	2.6

Important prescribing considerations

Interstitial pneumonitis

Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. A small study in Japanese subjects showed that 8 of 47 patients (17%) developed interstitial pneumonitis. Reports of interstitial changes including pulmonary fibrosis that led to hospitalization and death have been reported rarely post-marketing. Symptoms included exertional dyspnea, cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitual changes, and pulmonary function tests revealed a restrictive pattern with decreased Dl_{co}. Most cases occurred within the first 3 months of treatment with NILANDRON, and most reversed with discontinuation of therapy. A routine chest X-ray should be performed prior to initiating treatment with NILANDRON. Baseline pulmonary function tests may be considered. Patients should be instructed to report any new or worsening shortness of breath that they experience while on NILANDRON. **If symptoms occur, NILANDRON should be immediately discontinued until it can be determined if the symptoms are drug related.**

Hepatitis

Rare cases of death or hospitalization due to severe liver injury have been reported post-marketing in association with the use of NILANDRON. Hepatotoxicity in these reports generally occured within the first 3 to 4 months of treatment. Hepatitis or marked increase in liver enzymes leading drug discontinuation occurred in 1% of NILANDRON patients in controlled clinical trials.

**Based on maintenance dosage.*

day therapy for patients

Serum transaminase levels should be measured prior to starting treatment with NILANDRON, at regular intervals for the first 4 months of treatment, and periodically thereafter. Liver function tests should also be obtained at the first sign or symptom suggestive of liver dysfunction, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, NILANDRON should be immediately discontinued with close followup of liver function tests until resolution.

Use in Women

NILANDRON has no indication for women, and should not be used in this population.

- The most common noncastration-related adverse event was visual disturbance (usually delayed adaptation to dark), which led to withdrawal in 1% to 2% of patients[4]
  - –Patients experiencing visual disturbances should be cautioned about driving at night and advised to wear tinted glasses to reduce adaptation problems

Visual disturbances are generally mild and tend to disappear spontaneously or after planned dosage reduction[2]

Dose-related incidence of visual disturbances[4]

- The incidence rate of delayed adaptation to darkness with the 150 mg dose was 3.6%, while the incidence rate with the 300 mg dose was 9.3%
- Of patients reporting delayed adaptation to darkness, 71% experienced it during the first month of therapy

Mild: Awareness of symptoms, but symptoms easily tolerated.

Moderate: Enough discomfort to cause interference with usual activities.

Severe: Incapacitating, with inability to work and do usual activity.

Occurrence of delayed adaptation to darkness[4]

	Nilandron + Orchiectomy (n=225)	Placebo + Orchiectomy (n=232)
Mild	18 (8.0%)	1 (0.4%)
Moderate	11 (4.9%)	2 (0.9%)
Severe	0	0
Total	29 (12.9%)	3 (1.3%)

ONCE-A-DAY

Nilandron®

(nilutamide)

An Affordable, Once-Daily Antiandrogen That Significantly Extends Life

Please see complete prescribing information including boxed WARNING on page 10.

Well-tolerated one tablet once a day therapy for patients with advanced prostate cancer*

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

Important Prescribing Considerations

Interstitial pneumonitis

Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. A small study in Japanese subjects showed that 8 of 47 patients (17%) developed interstitial pneumonitis. Reports of interstitial changes including pulmonary fibrosis that led to hospitalization and death have been reported rarely post - marketing. Symptoms included exertional dyspnea, cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitial changes, and pulmonary function tests revealed a restrictive pattern with decreased $D1_{CO}$. Most cases occurred withing the first 3 months of treatments with NILANDRON, and most reversed with discontinuation of therapy. A routine chest X-ray should be performed prior to initiating treatment with NILANDRON. Baseline pulmonary function test may be considered. **Patients should be instructed to report any new or worsening shortness of breath that they experience while on NILANDRON.** If symptoms occur, NILANDRON should be immediately discontinued until it can be determined if the symptoms are drug related.

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Please see accompanying full prescribing information including boxed WARNING.

*Based on maintenance dosage.

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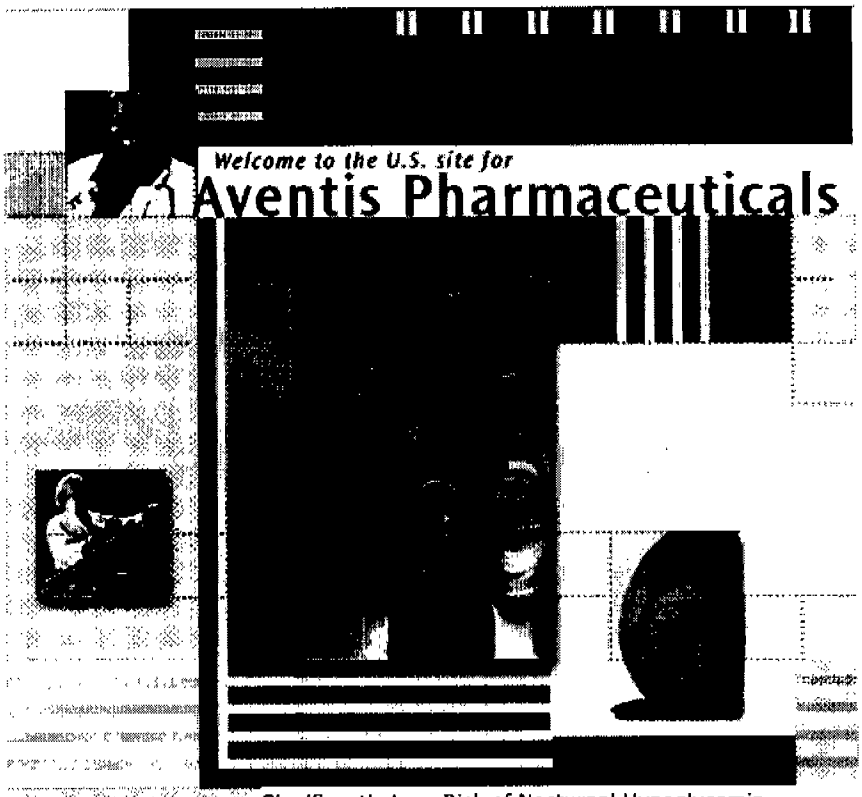

NEWS

Significantly Less Risk of Nocturnal Hypoglycemia Associated With LANTUS® (insulin glargine [rDNA origin] injection) Compared With NPH

This site intended for use by U.S. residents only

Last updated: 04/06/2001

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(pentoxifylline)
Prescribing Information

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Last Updated: 03/05/01

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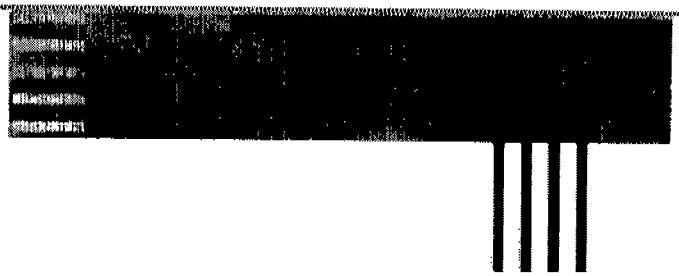

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PRODUCT OVERVIEW:
NILANDRON® (nilutamide)

- Nilandron® (nilutamide) is a once-daily, oral, nonsteroidal antiandrogen for the treatment of advanced prostate cancer.
- Nilandron is indicated for use in combination with orchiectomy (surgical removal of the testicles) for the treatment of advanced prostate cancer. For maximum benefit, Nilandron must be started on the same day as or on the day after surgery.
- In clinical studies, Nilandron showed statistically significant improvements in bone pain, a common complication of end-state prostate cancer.
- Clinical studies show that Nilandron increases the time to disease progression and increases overall survival time.
- Clinical studies demonstrated that Nilandron improves complete and/or partial disease regression.
- Nilandron is supplied as 50-mg tablets. The recommended starting dose is 300 mg once a day for the first 30 days and a total daily dose of 150 mg thereafter.
- Nilandron is generally well tolerated, and is associated with a low incidence of diarrhea.
- The most common side effects that occurred more often with Nilandron than placebo include: hot flushes (28.4%), impaired adaptation to dark (12.9%), nausea (9.8%), constipation (7.1%), and dizziness (7.1%).
    - The most common non-castration-related adverse event was visual disturbance (usually delayed adaptation to dark), which led to withdrawal in 1% to 2% of patients. Patients experiencing visual disturbances should be cautioned about driving at night and advised to wear tinted glasses to reduce adaptation problems.
    - Interstitial pneumonitis has been reported in 2% of Nilandron patients. A routine baseline chest x-ray should be taken before treatment and therapy should be interrupted at the first sign of dyspnea.
    - Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in 1% of Nilandron patients in controlled clinical trials. Transaminases should be monitored and treatment discontinued if these levels exceed 2 to 3 times the upper limit of normal.

Contact:
Charles F. Rouse III
Aventis Pharmaceuticals

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Last updated: 04/09/2001

3451T9

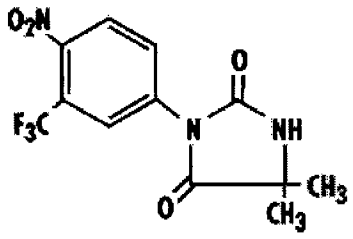
Nilandron® (nilutamide)

Prescribing Information as of September 1996

NILANDRON™
(nilutamide)
Tablets

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.

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 50 mg nilutamide. Other ingredients in NILANDRON tablets are corn starch, lactose, providone, docusate sodium, magnesium stearate, and talc.

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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 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}-∞obtained from the first dose of 3 x 50 mg. 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%

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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.

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CONTRAINDICATIONS:

NILANDRON tablets are contraindicated in patients:

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

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WARNINGS:

Interstitial pneumonitis

Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. Patients typically presented with progressive exertional dyspnea, and possibly with cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitial changes. The suggestive signs of pneumonitis most often occurred within the first

three months of NILANDRON treatment.

A routine chest X-ray should be performed before treatment, and patients should be told to report immediately any dyspnea or aggravation of pre-existing dyspnea.

At the onset of dyspnea or worsening of pre-existing dyspnea at any time during treatment, NILANDRON should be interrupted until it can be determined if respiratory symptoms are drug related. A chest X-ray should be obtained, and if there are findings suggestive of interstitial pneumonitis, treatment with NILANDRON should be discontinued. The pneumonitis is almost always reversible when treatment is discontinued.

If the chest X-ray appears normal, pulmonary function tests including DL_{CO} (diffusing capacity of the lung for carbon monoxide) should be performed. If a significant decrease of DL_{CO} and/or a restrictive pattern is observed on pulmonary function testing, NILANDRON treatment should be terminated. In the absence of chest X-ray and pulmonary function test findings consistent with interstitial pneumonitis, treatment with NILANDRON can be restarted under close monitoring of pulmonary symptoms.

Because interstitial pneumonitis was reported in 8 of 47 patients (17%) in a small study performed in Japan, specific caution should be observed in the treatment of Asian patients.

Hepatitis

Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in 1% of NILANDRON patients in controlled clinical trials:

Serum hepatic enzyme levels should be measured at baseline and at regular intervals (3 months); if transaminases increase over 2-3 times the upper limit of normal, treatment should be discontinued.

Appropriate laboratory testing should be done at the first symptom/sign of liver injury (e.g., jaundice, dark urine, fatigue, abdominal pain, or unexplained gastrointestinal symptoms) and NILANDRON treatment must be discontinued immediately if transaminases exceed 3 times the upper limit of normal.

There has been a report of elevated hepatic enzymes followed by death in a 65-year-old patient being treated with nilutamide.

Other

Foreign postmarketing surveillance has revealed isolated cases of aplastic anemia in which a causal relationship with NILANDRON could not be ascertained.

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PRECAUTIONS:

Information for Patients

Patients should be informed that NILANDRON tablets should be started on the day of, or on

the day after, surgical castration. They should also be informed that they should not interrupt their dosing of NILANDRON or stop taking this medication without consulting their physician.

Because of the possibility of interstitial pneumonitis, patients should also be told to report immediately any dyspnea or aggravation of pre-existing dyspnea.

Because of the possibility of hepatitis, patients should be told to consult with their physician should nausea, vomiting, abdominal pain, or jaundice occur.

Because of the possibility of an intolerance to alcohol (facial flushes, malaise, hypotension) following ingestion of NILANDRON, it is recommended that intake of alcoholic beverages be avoided by patients who experience this reaction. This effect has been reported in about 5% of patients treated with NILANDRON.

In clinical trials, 13% to 57% of patients receiving NILANDRON reported a delay in adaptation to dark, ranging from seconds to a few minutes, when passing from a lighted area to a dark area. This effect sometimes does not abate as drug treatment is continued. Patients who experience this effect should be cautioned about driving at night or through tunnels. This effect can be alleviated by the wearing of tinted glasses.

Drug Interactions

In vitro, nilutamide has been shown to inhibit the activity of liver cytochrome P-450 isoenzymes and, therefore, may reduce the metabolism of compounds requiring these systems.

Consequently, drugs with a low therapeutic margin, such as vitamin K antagonists, phenytoin, and theophylline, could have a delayed elimination and increases in their serum half-life leading to a toxic level. The dosage of these drugs or others with a similar metabolism may need to be modified if they are administered concomitantly with nilutamide. For example, when vitamin K antagonists are administered concomitantly with nilutamide, prothrombin time should be carefully monitored and, if necessary, the dosage of vitamin K antagonists should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of nilutamide to rats for 18 months at doses of 0, 5, 15, or 45 mg/kg/day produced benign Leydig cell tumors in 35% of the high-dose male rats (AUC exposures in high-dose rats were approximately 1 - 2 times human AUC exposures with therapeutic doses). The increased incidence of Leydig cell tumors is secondary to elevated luteinizing hormone (LH) concentrations resulting from loss of feedback inhibition at the pituitary. Elevated LH and testosterone concentrations are not observed in castrated men receiving NILANDRON. Nilutamide had no effect on the incidence, size, or time of onset of any spontaneous tumor in rats.

Nilutamide displayed no mutagenic effects in a variety of in vitro and in vivo tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests).

In reproduction studies in rats, nilutamide had no effect on the reproductive function of males and females, and no lethal, teratogenic, or growth-suppressive effects on fetuses were found. The maximal dose at which nilutamide did not affect reproductive function in either sex or have an effect on fetuses was estimated to be 45 mg/kg orally (AUC exposures in rats approximately 1-2 times human therapeutic AUC exposures).

Pregnancy

Pregnancy Category C; Animal reproduction studies have not been conducted with nilutamide. It is also not known whether nilutamide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Nilutamide should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been determined.

Animal Pharmacology and Toxicology

Administration of NILANDRON to beagle dogs resulted in drug-related deaths at dose levels that produce AUC exposures in dogs much lower than the AUC exposures of men receiving the therapeutic doses of 150 and 300 mg/day. Nilutamide-induced toxicity in dogs was cumulative with progressively lower doses producing death when given for longer durations. Nilutamide given to dogs at 60 mg/kg/day (1-2 times human AUC exposure) for 1 month produced 100% mortality. Administration of 20 and 30 mg/kg/day nilutamide (1/2-1 times human AUC exposure) for 6 months resulted in 20% and 70% mortality in treated dogs. Administration to dogs of 3, 6, and 12 mg/kg/day nilutamide (1/10-1/2 human AUC exposure) for 1 year resulted in 8%, 33%, and 50% mortality, respectively. **A "no-effect level" for nilutamide-induced mortality in dogs was not identified.** Pathology data from the one-year oral toxicity study suggest that the deaths in dogs were secondary to liver toxicity. Marked-to-massive hepatocellular swelling and vacuolization were observed in affected dogs. Liver toxicity in dogs was not consistently associated with elevations of liver enzymes.

Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1-2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis).

The hepatic and pulmonary adverse effects observed in nilutamide-treated animals and men are similar to effects observed with another nitroaromatic compound, nitrofurantoin. Nilutamide and nitrofurantoin are both metabolized in vitro to nitroanion free-radicals by microsomal NADPH-cytochrome P450 reductase in the lungs and liver of rats and humans.

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ADVERSE REACTIONS:

The following adverse experiences were reported during a multicenter clinical trial comparing NILANDRON + surgical castration versus placebo + surgical castration. The most frequently reported (greater than 5%) adverse experiences during treatment with NILANDRON tablets in combination with surgical castration are listed below. For comparison, adverse experiences seen with surgical castration and placebo are also listed.

Adverse Experience	NILANDRON + surgical castration (N=225) % All	Placebo + surgical castration (N=232) % All
Cardiovascular System		
Hypertension	5.3	2.6
Digestive System		
Nausea	9.8	6.0
Constipation	7.1	3.9
Endocrine System		
Hot flushes	28.4	22.4
Metabolic and Nutritional System		
Increased AST	8.0	3.9
Increased ALT	7.6	4.3
Nervous System		
Dizziness	7.1	3.4
Respiratory System		
Dyspnea	6.2	7.3
Special Senses		
Impaired adaptation to dark	12.9	1.3
Abnormal vision	6.7	1.7
Urogenital System		
Urinary tract infection	8.0	9.1

The overall incidence of adverse experiences was 86% (194/225) for the NILANDRON group and 81% (188/232) for the placebo group.

The following adverse experiences were reported during a multicenter clinical trial comparing NILANDRON + leuprolide versus placebo + leuprolide. The most frequently reported (greater than 5%) adverse experiences during treatment with NILANDRON tablets in combination with leuprolide are listed below. For comparison, adverse experiences seen with leuprolide and placebo are also listed.

Adverse Experience	NILANDRON + leuprolide (N=209) % All	Placebo + leuprolide (N=202) % All
Body as a Whole		
Pain	26.8	27.7
Headache	13.9	10.4
Asthenia	19.1	20.8
Back pain	11.5	16.8

Abdominal pain	10.0	5.4
Chest pain	7.2	4.5
Flu syndrome	7.2	3.0
Fever	5.3	6.4
Cardiovascular System		
Hypertension	9.1	9.9
Digestive System		
Nausea	23.9	8.4
Constipation	19.6	16.8
Anorexia	11.0	6.4
Dyspepsia	6.7	4.5
Vomiting	5.7	4.0
Endocrine System		
Hot flushes	66.5	59.4
Impotence	11.0	12.9
Libido decreased	11.0	4.5
Hemic and Lymphatic System		
Anemia	7.2	6.4
Metabolic and Nutritional System		
Increased AST	12.9	13.9
Peripheral edema	12.4	17.3
Increased ALT	9.1	8.9
Musculo Skeletal System		
Bone Pain	6.2	5.0
Nervous System		
Insomnia	16.3	15.8
Dizziness	10.0	11.4
Depression	8.6	7.4
Hypesthesia	5.3	2.0
Respiratory System		
Dyspnea	10.5	7.4
Upper respiratory infection	8.1	10.9
Pneumonia	5.3	3.5
Skin and Appendages		
Sweating	6.2	3.0
Body hair loss	5.7	0.5
Dry skin	5.3	2.5
Rash	5.3	4.0
Special Senses		
Impaired adaptation to dark	56.9	5.4
Chromatopsia	8.6	0.0
Impaired adaptation to light	7.7	1.0
Abnormal vision	6.2	4.5
Urogenital System		
Testicular atrophy	16.3	12.4
Gynecomastia	10.5	11.9
Urinary tract infection	8.6	21.3
Hematuria	8.1	7.9
Urinary tract disorder	7.2	10.4
Nocturia	6.7	6.4

The overall incidence of adverse experiences is 99.5% (208/209) for the NILANDRON group and 98.5% (199/202) for the placebo group.

Some frequently occurring adverse experiences, for example hot flushes, impotence, and decreased libido, are known to be associated with low serum androgen levels and known to occur with medical or surgical castration alone. Notable was the higher incidence of visual disturbances (variously described as impaired adaptation to darkness, abnormal vision, and colored vision), which led to treatment discontinuation in 1% to 2% of patients.

Interstitial pneumonitis occurred in one (<1%) patient receiving NILANDRON in combination with surgical castration and in seven patients (3%) receiving NILANDRON in combination with leuprolide and one patient receiving placebo in combination with leuprolide. Overall, it has been reported in 2% of patients receiving NILANDRON. This included a report of interstitial pneumonitis in 8 of 47 patients (17%) in a small study performed in Japan.

In addition, the following adverse experiences were reported in 2 to 5% of patients treated with NILANDRON in combination with leuprolide or orchiectomy.

Body as a Whole: Malaise (2%).

Cardiovascular System: Angina (2%), heart failure (3%), syncope (2%).

Digestive System: Diarrhea (2%), gastrointestinal disorder (2%), gastrointestinal hemorrhage (2%), melena (2%).

Metabolic and Nutritional System: Alcohol intolerance (5%), edema (2%), weight loss (2%).

Musculoskeletal System: Arthritis (2%).

Nervous System: Dry mouth (2%), nervousness (2%), paresthesia (3%).

Respiratory System: Cough increased (2%), interstitial lung disease (2%), lung disorder (4%), rhinitis (2%).

Skin and Appendages: Pruritus (2%).

Special Senses: Cataract (2%), photophobia (2%).

Laboratory Values: Haptoglobin increased (2%), leukopenia (3%), alkaline phosphatase increased (3%), BUN increased (2%), creatinine increased (2%), hyperglycemia (4%).

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OVERDOSAGE:

One case of massive overdosage has been published. A 79-year-old man attempted suicide by ingesting 13 g of nilutamide (i.e., 43 times the maximum recommended dose). Despite immediate gastric lavage and oral administration of activated charcoal, plasma nilutamide levels peaked at 6 times the normal range 2 hours after ingestion. There were no clinical signs or symptoms or changes in parameters such as transaminases or chest X-ray. Maintenance treatment (150 mg/day) was resumed 30 days later.

In repeated-dose tolerance studies, doses of 600 mg/day and 900 mg/day were administered to 9 and 4 patients, respectively. The ingestion of these doses was associated with gastrointestinal disorders, including nausea and vomiting, malaise, headache, and dizziness. In addition, a transient elevation in hepatic enzyme levels was noted in one patient.

Since nilutamide is protein bound, dialysis may not be useful as treatment for overdose. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

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DOSAGE AND ADMINISTRATION:

The recommended dosage is six tablets (50 mg each) once a day for a total daily dose of 300 mg for 30 days followed thereafter by three tablets (50 mg each) once a day for a total daily dosage of 150 mg. NILANDRON tablets can be taken with or without food.

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HOW SUPPLIED:

White, biconvex (with a triangular logo on one face and an internal reference number [168] on the other), cylindrical (about 7 mm in diameter) NILANDRON tablets containing 50 mg of nilutamide are available in "child-resistant" PVC blister pack with an aluminum foil backing in boxes of 90 tablets (6 blisters of 15 tablets each) NDC 0088-1110-35

Store at room temperature between 15°C and 30°C (59° and 86°F). Protect from light.

Prescribing Information as of September 1996

Manufactured by Usiphar, 60200 Compiegne, France for:
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Kansas City, MO 64137 USA

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