PRODUCT MONOGRAPH

[Pr]ANANDRON®

(nilutamide)

Tablets
50 mg

Nonsteroidal Antiandrogen

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ACTION AND CLINICAL PHARMACOLOGY

Nilutamide is a pure, nonsteroidal antiandrogen which blocks androgens binding at receptor target cells. Nilutamide is specific and does not bind to any other steroidal receptors; therefore, it does not have any other hormonal or antihormonal activity.

Nilutamide demonstrates potent antiandrogenic effects by inhibiting androgen uptake and/or inhibiting nuclear binding of androgen in target tissues. In adult male rats, ventral prostate and seminal vesicle weights were markedly reduced by daily administration of nilutamide.

Androgen-sensitive prostatic carcinoma cells respond to treatment that counteracts the effect of androgen and/or removes the source of androgen e.g. castration. Combined with castration, nilutamide exerts a total peripheral antiandrogenic activity by antagonizing the action of androgens of adrenal origin which otherwise may maintain the proliferation of prostatic cancer cells.

Nilutamide also inhibits the consequences of the initial rise of testosterone plasma levels observed after treatment with LH-RH agonists.

Clinical studies with ANANDRON (nilutamide) have demonstrated improvement in metastatic bone pain, diminished consumption of analgesics, regression of the cancer together with reduced rate of objective progression and higher survival actuarial rate of patients with metastatic prostate cancer.

Nilutamide is rapidly and completely absorbed as indicated by the low level of fecal radioactivity measured after administration of radiolabelled nilutamide. Unchanged nilutamide represents the major active compound. In patients, nilutamide has a long half-life of 56 hours (range from 23 to 87 hours). Nilutamide is 84% bound to plasma proteins. The plasma concentrations are dose-related and steady-state levels are reached approximately 2 weeks after initiation of treatment. No evidence of accumulation has been demonstrated.

Nilutamide is mainly excreted in the urine as metabolites. Using radiolabelled nilutamide, unchanged drug accounts for only 3% of recovered urinary radioactivity. Fecal excretion accounts for 1.4 to 7% of the total administered dose after 4-5 days. The major metabolic pathway is by reduction of the nitro group and the amino derivative of nilutamide represents the

major metabolite. Among the metabolites of nilutamide only the hydroxymethylnitro derivative shows some androgen receptor binding affinity.

INDICATIONS AND CLINICAL USE

ANANDRON (nilutamide) is indicated in the treatment of metastatic prostatic carcinoma (Stage D_2) in conjunction with surgical castration.

CONTRAINDICATIONS

ANANDRON (nilutamide) is contraindicated in:

- patients with known hypersensitivity to the drug, or to any constituents of the drug product
- patients with severe hepatic dysfunction
- patients with severe respiratory insufficiency
- women and children.

WARNINGS

The hepatic and respiratory state of the patient should be evaluated and the necessity to report any respiratory symptoms as soon as they appear should be emphasized.

Cases of interstitial lung disease such as pneumonitis and pulmonary fibrosis have been reported with the use of ANANDRON (nilutamide). Some cases of pulmonary fibrosis were fatal. Baseline imaging (eg. chest X-ray) should be performed prior to therapy. Baseline pulmonary function tests may be considered (see CONTRAINDICATIONS, Monitoring and Laboratory Tests, and PRECAUTIONS). In the event of dyspnea or worsening of pre-existing dyspnea, treatment with ANANDRON should be discontinued and appropriate medical treatment should be initiated. If interstitial lung disease is diagnosed, ANANDRON must be discontinued to reduce the risk of progression to pulmonary fibrosis; corticosteroid treatment may be considered.

Cases of hepatic dysfunction have been reported with the use of ANANDRON. If clinical symptoms give rise to a suspicion of liver dysfunction, transaminases should be measured. If an increase in serum transaminases above three times the upper limit of normal laboratory range is shown, treatment must be interrupted.

Antiandrogen Withdrawal Syndrome

In some patients with metastatic prostate cancer, antiandrogens (steroidal or non-steroidal), may promote, rather than inhibit, the growth of prostate cancer. A decrease in PSA and/or clinical improvement following the discontinuation of antiandrogens have been reported. It is recommended that patients prescribed an antiandrogen, who have PSA progression, should have the antiandrogen discontinued immediately and be monitored for 6 to 8 weeks for a withdrawal response prior to any decision to proceed with other prostate cancer therapy.

Cardiovascular

There may be a relationship between combined androgen blockade and cardiovascular risk in men with prostate cancer on the basis of the demonstrated adverse impact of androgen deprivation on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity (see REFERENCES section). Reports of events related to cardiovascular ischemia including myocardial infarction and cardiovascular-related deaths have been received in patients treated with combined androgen blockade.

Physicians should consider whether the benefits of combined androgen blockade outweigh the potential cardiovascular risk. Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered (see "Monitoring and Laboratory Test" below).

Effect on QT/QTc interval
Combined androgen blockade has the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of combined androgen blockade outweigh the potential risk in patients with electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications. (See PRECAUTIONS, Drug-Drug interactions)

ANANDRON should not be administered to patients with congenital long QT syndrome and should be discontinued in patients that develop QT prolongation during treatment.

Endocrine and Metabolism

A reduction in glucose tolerance and an increased risk in developing diabetes have been reported in men treated with combined androgen blockade. Patients treated with combined androgen blockade should undergo periodic monitoring of blood glucose. Diabetic patients may require more frequent monitoring when receiving ADT.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Musculoskeletal

Changes in bone density:
Decreased bone mineral density can be anticipated with long term use of an antiandrogen. Combined androgen blockade is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal bone fracture increases with the duration of combined androgen blockade. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, ANANDRON may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with ANANDRON is instituted.

Monitoring and Laboratory Tests

Baseline risk factors of cardiovascular diseases should be assessed. Patients should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. Evaluation for QT prolongation should be undertaken for patients at risk by baseline ECG recording and frequently during treatment in patients also taking medicinal products known to prolong the QTc interval or to induce torsades de pointes. In addition, as electrolyte abnormalities may prolong the QT interval, baseline measurements of serum electrolytes, including potassium, calcium, and magnesium levels, are recommended (See WARNINGS, Cardiovascular and PRECAUTIONS, Drug-Drug Interactions).

Monitoring of the hepatic function is also recommended.

Blood glucose levels and/or glycosylated hemoglobin (HbA1c) should be checked periodically in patients treated with androgen deprivation therapy and more frequently in diabetic patients (see Endocrine and Metabolism).

The effects of nilutamide on bone mineral density may be monitored by bone scans.

Baseline imaging (e.g. chest X-ray) and monitoring of pulmonary function is recommended (see CONTRAINIDICATIONS, WARNINGS and PRECAUTIONS).

PRECAUTIONS

Information for Patients

Patients should be informed that they should not interrupt their dosing or stop taking ANANDRON (nilutamide) without consulting their physician(s).

Where patients are participating in activities such as driving automobile or operating machinery, attention should be drawn to possible visual disturbances mainly due to an increase in adaptation time when passing from a well lit area to a more dimly lit area. These disturbances, should they occur, can decrease even if treatment is continued and can be ameliorated with the use of sunglasses.

Patients should be informed about signs / symptoms suggestive of liver dysfunction (e.g. right upper quadrant tenderness, dark urine, persistent anorexia, nausea, vomiting, jaundice, pruritus or unexplained flu-like symptoms) and be advised to contact their physician should these occur.

Patients administered nilutamide should be warned against consuming alcohol because of a possible disulfiram-like reaction.

Patients should be instructed to report any new or worsening shortness of breath. If symptoms occur, ANANDRON should be discontinued and appropriate medical treatment initiated.

Use in Specific Patient Populations

In an uncontrolled pilot study conducted in a Japanese population, interstitial pneumonitis was reported and was considered possibly or probably related to nilutamide in 6 out of 47 patients (12.8%). This incidence figure is higher than the incidence of interstitial pneumonitis available from the international database of placebo-controlled trials in orchiectomized patients (1.1%; see ADVERSE REACTIONS section). In concurrent pharmacokinetics/metabolism investigations in Japanese vs. Caucasian patients, no differences in the results could account for the higher incidence of this event in this race. The incidence rate of raised transaminases in the Japanese study was 19%. Special care should be observed when treating Asian patients.

DRUG-DRUG INTERACTIONS

Nilutamide, apparently through an effect on certain oxidative microsomal enzymes, may reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, lidocaine, diazepam and theophylline, thereby delaying elimination and increasing blood levels of these drugs. Benzodiazepines that are not oxidized by the hepatic system do not exhibit this effect.

Dosage of the drugs mentioned above, and other similarly metabolized drugs, may require adjustment when starting or stopping concomitantly administered nilutamide to maintain safe optimum therapeutic blood levels.

In case of associated treatment with warfarin-type anticoagulants, close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary.

Alcohol intolerance (disulfiram-like reaction) may occur if alcohol is consumed during treatment with nilutamide.

Since combined androgen blockade may prolong the QTc interval, the concomitant use of ANANDRON with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

In case of ANANDRON treatment in combination with such medicinal products, the QT interval should be closely monitored.

ADVERSE REACTIONS

CLINICAL TRIALS

Adverse Drug Reactions

The following table lists the possibly or probably drug-related adverse events (adverse reactions) most frequently reported during placebo-controlled clinical trials of ANANDRON (nilutamide) in conjunction with surgical castration. Hot flushes, decreased libido, impotence and body hair loss are known to occur with surgical castration.

	Percentage of patients	
	Nilutamide	**Placebo**
Adverse reaction	**(N= 560)**	**(N= 558)**
Hot Flushes	13.8	9.7
Impaired Adaptation to Darkness	10.5	0.7
Nausea	4.3	1.1
Alcohol Intolerance	4.1	0.2
Dizziness	2.9	0.5
Chromatopsia	2.5	0
SGPT Increased	2.0	0.7
Abnormal Vision	1.8	0.5
SGOT Increased	1.4	0.4
Photophobia	1.4	0
Hyperglycemia	1.3	1.6
Impotence	1.3	0.5
Dyspnea	1.1	0.2
Gynecomastia	1.1	1.3
Impaired Light Adaptation	1.1	0
Interstitial Lung Disease	1.1	0
Eye Disorder	0.9	0.4
Libido Decreased	0.9	0
Sweating Increased	0.9	0.5
Vomiting	0.9	0
Anorexia	0.7	0
Blurred vision	0.7	0
Hepatitis	0.7	0
Hypertension	0.7	0.2
Anemia	0.5	0.2
Asthenia	0.5	0.4
Gastrointestinal Pain	0.5	0.2
Lung Disorder	0.5	0
Malaise	0.5	0

Adverse Events Irrespective of Relationship with Nilutamide

Other adverse events reported overall in clinical trials (of which most occurred with similar frequencies in patients receiving placebo), others known to commonly occur in elderly patients or expected in patients with metastatic prostate cancer included:

Cardiovascular system:	Cerebrovascular accident (1.4%), heart failure (1.0%). Rare cases of tachycardia.
Digestive system:	Constipation (2.6%), gastrointestinal disorder (2.0%). Rare cases of diarrhea.
Metabolic and nutritional system:	Peripheral edema (1.5%).
Nervous system:	Headache (2.6%), depression (1.1%), insomnia (1.1%). Rare cases of drowsiness and anxiety.
Skin and appendages:	Pruritus (1.1%). Rare cases of maculopapular rash and hirsutism.
Special senses:	Rare cases of dazzle and dry mouth.
Urogenital system:	Urinary tract infection (1.3%).

No causal relationship of these experiences with drug treatment has been established.

Post-Marketing Surveillance

The adverse events which have been spontaneously reported worldwide further to marketing of ANANDRON and which are considered possibly or probably related to the drug (adverse reactions) include the following: interstitial lung disease (including interstitial pneumonitis and pulmonary fibrosis, which may be fatal), hepatocellular or mixed liver injury, fulminant hepatitis, and unspecified vision disorders. Isolated cases of angina pectoris, anxiety dyspnea palpitation, cold extremities, dizziness headache, gynecomastia, maculopapular rash, QT prolongation, urticaria, vomiting and weight increase have been reported.

Aplastic anemia (including one fatality) has been reported rarely in patients treated with ANANDRON but no specific relationship to the drug product has been ascertained.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

At the dose of 900 mg (3 to 6 times the recommended daily dose), ANANDRON (nilutamide) caused malaise, dizziness, nausea and vomiting which disappeared upon discontinuation of treatment.

The effects of ingestion of a very high dose of ANANDRON have been described in one case report. A 79 year old man was admitted 2 hours after the ingestion of 13 g of nilutamide (170 mg/kg or 43 times the therapeutic dose). He had been receiving nilutamide 300 mg/day for two weeks. On admission, he underwent gastric lavage immediately, followed by administration of a 20 g oral dose of activated charcoal. Clinical and biological parameters were monitored. There were no changes in the biological parameters as compared to the pre-treatment values either early post ingestion or upon control on day 4, 9 and 30. The clinical manifestations were limited to moderate vomiting and diarrhea during the first 12 hours post ingestion and the patient recovered. Plasma and serum concentrations were measured. The initial level reached 6 times the usual therapeutic range of 4.4-8.5 mg/L. Levels 3.5 times greater than the normal range were measured 72 hours post-ingestion.

The ingested dose (170 mg/kg) is close to the lethal dose in animals, the oral LD_{50} being 215 mg/kg (180-240) in mice and 195 mg/kg (160-230) in rats. However, the extent of absorption was probably limited by early therapeutic intervention. The lethal dose in man has not been established.

DOSAGE AND ADMINISTRATION

Treatment with ANANDRON (nilutamide) should be initiated immediately after surgical castration.

Initial dosage:	300 mg once daily for the first month of treatment.
Maintenance dosage:	Maintenance treatment may be started earlier should intolerance occur. 150 mg once daily.

ANANDRON should be taken before breakfast, until more information is available.

Discontinuation of ANANDRON should be considered once objective evidence of disease progression is noted.

PHARMACEUTICAL INFORMATION

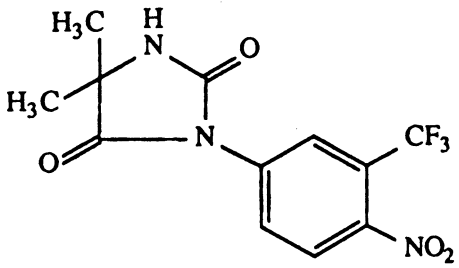
DRUG SUBSTANCE

Trade Name ANANDRON®

Proper Name nilutamide

Chemical Name 5,5-Dimethyl-3-(α, α, α - trifluoro-4-nitro-m-tolyl) hydantoin

Structural Formula



Molecular Formula $C_{12}H_{10}F_3N_3O_4$

Molecular Weight 317.25

Description White to off-white powder. It is soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane and methanol. It is very slightly soluble in water (< 0.1% w/v) at 25°C. It melts between 153°C and 156°C.

Composition ANANDRON tablets contain 50 mg nilutamide as active drug substance. Non-medicinal ingredients are: lactose, corn starch, sodium docusate, talc, povidone and magnesium stearate.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 and 30°C. Protect from light, heat and humidity.

AVAILABILITY OF DOSAGE FORMS

ANANDRON (nilutamide) 50 mg tablets are white, cylindrical, biconvex tablets, debossed with "**168**" over "**A**" on one side and with the Roussel logo on the other side.

They are packaged in boxes of 90 (3 x 30 blister-packed) tablets.

INFORMATION FOR THE PATIENT

How to make ANANDRON work best for you

Your doctor has decided that ANANDRON is the best treatment for you. Remember that the chances of controlling your illness are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This leaflet is intended to provide you with only brief advice about ANANDRON tablets. It does not take the place of your doctor's advice or your pharmacist's advice. Your doctor knows and understands your personal condition; be sure to follow your doctor's instructions carefully and read any materials he gives you. If you have any questions after reading this information leaflet, be sure to ask your doctor or pharmacist. Please note that both your doctor and pharmacist have much more information about ANANDRON than the information contained in this brief leaflet.

Keep this leaflet with the medicine as you may need to use it again.

What is ANANDRON and how does it work?

ANANDRON belongs to a group of medicines called "antiandrogens". It blocks the effect of hormones called androgens, which are naturally produced by your body. By blocking the effect of androgens, ANANDRON may help slow down the disease in your prostate gland. It will also help to reduce the symptoms you experience because of this disease.

What does ANANDRON contain?

ANANDRON tablets contain the active ingredient nilutamide. Each tablet contains 50 mg of nilutamide. ANANDRON tablets contain lactose.

ANANDRON tablets are white to off-white in colour and are debossed with "**168**" over "**A**" on one side and with the Roussel logo on the other side.

How should you take ANANDRON to make it work best for you?

- Take ANANDRON tablets exactly as your doctor has told you. Do not take more or less of it. Do not take it more often. Do not take it for a longer period of time than your doctor ordered.
- Take your dose by mouth, once a day before breakfast.
- The usual starting dose is 300 mg (6 tablets) per day for the first four weeks. Your dose of ANANDRON may then be decreased to 150 mg (3 tablets) every day.

Your doctor will decide your dose, your schedule, and for how long you need to take ANANDRON. This will depend on your disease condition and on whether you experience side-effects. Talk to your doctor if you have questions about this.

What to do if you miss a dose?

If you miss a dose, take it as soon as you remember and then resume your normal dosing schedule. However, you should not take more than 300 mg of ANANDRON in any one day during the first four weeks of treatment or more than 150 mg in any one day thereafter. Therefore, if it is almost time for your next dose when you remember that you have missed a dose, skip the dose you missed and take your next dose at the usual time (i.e. do not take a double dose). If you are concerned or if you have missed more than one dose, please speak to your doctor.

What to do if you take too many tablets?

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you take, by mistake, too many tablets on the same day, you may feel nauseous and dizzy, and you may vomit. These symptoms will normally go away after temporarily interrupting your treatment or reducing the dose, however these steps should only be taken on your doctor's advice. If you have taken more than 300 mg in one day, you should contact your doctor as soon as possible.

Does ANANDRON have side effects?

The various treatments of disease of the prostate, such as yours, can all cause hot flushes, decrease in sex drive, or impotence.

ANANDRON is usually well tolerated but like any other medicine, can cause side effects. Most side effects with ANANDRON occur early in the course of treatment and will usually lessen after four weeks when the dose is normally reduced to 150 mg daily.

The most common side effects affect the eyes. You may notice that your eyes require more time to adapt to darkness, especially when there is a sudden change in lighting (for example, driving through a tunnel). When it occurs, this problem is almost always temporary and may be improved by wearing tinted glasses. However, until your eyes accommodate better to the dark, you should be very careful when driving or operating machinery.

Some patients may develop breathing problems or a worsening of a pre-existing breathing problem. Symptoms may include shortness of breath, coughing, chest pain and fever. Fatal cases due to pulmonary problems have been reported during ANANDRON treatment. It is important that you contact your doctor immediately if you have any breathing difficulties while taking ANANDRON.

In rare cases, ANANDRON may cause an increase in liver tests and, very rarely, hepatitis. Symptoms that may suggest a liver problem include: persistent lack of appetite, nausea (queasiness), vomiting, abdominal pain or tenderness, jaundice (yellow eyes and/or skin), dark urine, itching or unexplained flu-like symptoms. You should advise your doctor promptly if you develop any of these symptoms.

ANANDRON can also cause nausea and vomiting which are not related to liver problems. It can also cause dizziness. In most cases, these symptoms will improve following dosage reduction which normally occurs after four weeks of treatment. However, you should inform your doctor as soon as possible if you experience vomiting because it may be preferable to lower your dose earlier.

You should talk to your doctor or pharmacist if you have severe bone pain during treatment with ANANDRON.

Tell a doctor or pharmacist if you feel a very fast, uneven or forceful heartbeat (palpitations), shortness of breath, chest discomfort, or if you feel faint during treatment with ANANDRON.

In some patients with metastatic prostate cancer, antiandrogen drugs, like ANANDRON may promote, rather than slow down, the disease. Your doctor may advise you to stop your treatment with ANANDRON in case of worsening of the disease. Your condition should be monitored prior starting a new treatment.

If you think that you are reacting badly to ANANDRON, please tell your doctor. This is especially important if you have any problem that is not mentioned in this leaflet.

Can you take ANANDRON with alcohol and other medicines?

Some patients being treated with ANANDRON may have hot flushes or feel unwell after drinking alcohol. This is known as alcohol intolerance. If this happens to you, you should avoid alcohol completely. Please contact your doctor or pharmacist for advice.

ANANDRON may interfere or cause problems with other medicines that you are taking, so it is important that you tell your doctor and pharmacist about all of the medicines that you are taking, including those you have obtained without a prescription.

Drugs that may interact with ANANDRON include, but are not limited to:

- drugs used to thin the blood, such as: warfarin or nicoumalone
- drugs used to treat epilepsy, such as: phenytoin
- drugs used to treat hypertension (high blood pressure), angina, migraine or other conditions, such as: propranolol
- anti-anxiety drugs, such as: chlordiazepoxide or diazepam
- anti-asthma drugs, such as: theophylline
- antiarrhythmic drugs (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antipsychotic drugs (used to treat mental disorders) such as: chlorpromazine
- antidepressant drugs (used to treat depression) such as: amitryptiline, nortryptiline

- opioid drugs, such as: methadone
- antibiotics, such as: erythromycin, clarithromycin, azithromycin, moxifloxacin
- antifungals
- antimalarials, such as: quinine
- drugs belonging to a class called beta-2 agonists, such as: salbutamol
- drugs belonging to a class called 5-HT3 antagonists, such as: ondansetron.

Your doctor will be able to advise you what to do if you are taking any of these medicines. Your doctor may also perform some blood tests.

What should you remember?

Before taking this medication tell your doctor and pharmacist if:

- you have previously been treated for your prostate condition with a hormone, and the treatment did not work;
- you have liver or breathing problems. You should not take ANANDRON if you have either a severe liver or severe breathing disorder. Please discuss this with your doctor if you believe that you have either of these conditions;
- you have lactose intolerance;
- you are taking any other medication;
- you have low red blood cell count (anemia);
- you have family history of severe osteoporosis, have low bone mineral density, if you are taking any medication that can cause thinning of the bones (such as corticosteroids or anti-convulsive (anti-seizure) medication), or if you use alcohol or tobacco. ANANDRON may increase your risk of bone thinning (osteoporosis) and bone fractures;
- you have heart disease, or a heart condition called “Long QT syndrome”;
- you have diabetes (high blood sugar). ANANDRON may affect your blood glucose level and you may need to test your blood sugar more frequently while taking ANANDRON;
- you have any other medical problem(s).

While taking this medication

- Report any unusual reactions to your doctor without delay. This is important as it will aid in the early detection and prevention of potential complications;
- ANANDRON is intended for the treatment of prostate disease in men and therefore should not be taken under any circumstances by women or by children;
- Keep ANANDRON at room temperature between 15 and 30°C. Protect the tablets from excessive heat, light and humidity. As with all medicines, you should store the tablets in the original pharmacist container and out of the reach of children;

- If you require more information on this drug, consult your doctor or pharmacist.

What else do you need to know?

Return any unused or expired ANANDRON tablets to your pharmacist for disposal.

PHARMACOLOGY

Animal Pharmacology

Nilutamide showed antiandrogenic effects at doses varying from 2 to 50 mg/kg in immature and adult castrated male rats administered 50 mcg/day of testosterone. Significant reductions in prostate and seminal vesicle weights were observed after 7 days of treatment. In the adults, 10 mg/kg of nilutamide given orally inhibited the effect of 50 mcg/day of testosterone on increases in prostate weight. In adult castrated male dogs the oral dose inhibiting 50% of the effect of testosterone (0.5 mg/kg/day) varied between 1 and 3 mg/kg/day.

In animal studies, nilutamide did not show any estrogenic or glucocorticoid activities nor any progestomimetic or antiprogesterone effects.

Nilutamide demonstrated no anticonvulsant or anticholinergic effects when given orally to mice at doses of 3 to 100 mg/kg.

Some analgesic and anti-inflammatory activities were observed in mice and rats administered doses of 100 mg/kg orally and not at lower doses of 3, 10 and 30 mg/kg.

In dogs given 1 and 3 mg/kg i.v. of nilutamide, no changes were observed on the cardiovascular or respiratory functions but some minor effects were observed at doses of 10 mg/kg.

No effect on the blood glucose level was shown in rats administered nilutamide orally at doses of 3 to 100 mg/kg.

Prolongation of the hexobarbital induced sleeping time, potentiation of amphetamine induced stereotypical behavior and potentiation of the anticoagulant effect of warfarin were observed in mice or rats given nilutamide concomitantly.

Human Pharmacology

Plasma hormone levels were measured over a 6-month period in a double-blind trial in which previously untreated patients with stage D prostatic carcinoma were orchiectomized and then immediately received either placebo, ANANDRON (nilutamide) 150 mg/day or ANANDRON 300 mg/day. Results have shown that nilutamide does not modify pituitary secretion in orchiectomized patients but lowers adrenal androgen concentrations apparently without influencing cortisol levels.

CLINICAL EXPERIENCE

A randomized, double-blind long term follow-up study was undertaken in order to compare the efficacy of orchiectomy combined with ANANDRON (nilutamide) to orchiectomy alone in the treatment of previously untreated patients with stage D_2 prostatic carcinoma. The dosage of ANANDRON was 300 mg OD for the first month and 150 mg OD thereafter.

Four hundred and fifty-seven (457) patients were enrolled in the study (232 in the placebo plus orchiectomy group and 225 in the ANANDRON plus orchiectomy group). At the time of

analysis, a significantly greater number of regressions (complete + partial) had been observed in patients treated with ANANDRON and orchiectomy than in patients treated with placebo and orchiectomy (41% versus 24%, $p<0.001$) at some time during the study (best objective response). Progression-free survival was significantly longer in the group treated by orchiectomy plus ANANDRON (20.8 months) than in the group of patients who underwent orchiectomy only (14.9 months) [p=0.005]. The median time to death from prostatic cancer was 37.0 months for the ANANDRON + orchiectomy group and 30.0 months for the placebo + orchiectomy group, a difference of 7 months. Significant differences in favor of the ANANDRON group were found at several intervals for improvement of bone pain, prostatic acid phosphatase, prostate specific antigen, alkaline phosphatase and bone scan isotope uptake.

TOXICOLOGY

Acute Toxicity

		LD_{50} (mg/kg)	
Species	**Sex**	**Oral**	**Intraperitoneal**
Rat	Male	195	135
	Female	210	125
Mouse	Male	215	180
	Female	200	150

Clinical signs of overdosage included hypotonicity, apathy, respiratory difficulties, lethargy, tremors, convulsions, lung congestion and hypothermia. Reduced body weight gain was observed after intraperitoneal administration.

Chronic Toxicity

Three hundred and twenty rats (160 per sex) were randomly assigned to 4 groups of 40 animals/sex/group. Nilutamide was given orally in doses of 0, 5, 15 and 45 mg/kg/day for 78 consecutive weeks. The distribution of mortality was comparable in all groups and the factors contributing to death did not indicate any treatment or dose relationship. The main observed clinical signs of toxicity were pallor of the eyes and piloerection. Hypotonicity was noted in all males at the high dose level. A dose-dependent reduction in body weight gain was observed in both sexes and appeared to be related to a decrease in food consumption. It was significant in the 45 mg/kg/day group. Ophthalmoscopic examinations revealed some lens opacities which were not considered treatment-related. Macroscopic examinations showed a dose-related reduction in the size and weight of the prostate and seminal vesicles of male animals. Other observed organ weight changes were not considered drug-related. In some male animals, a testicular enlargement was observed as a result of interstitial Leydig cell hyperplasia. Except for an increased incidence of benign Leydig cell tumors in males in the 45 mg/kg/day group, nilutamide did not demonstrate other tumorigenic potential. Hematology investigations showed a dose-related anemia in animals in the mid and high dose groups with significant decreases in hemoglobin, decreases in RBC count and packed cell volume and increases in MCV and reticulocyte count. Blood biochemistry evaluations revealed the following: increases in BUN, plasma creatinine, and albumin; decreases in α_1 and α_2 globulins and variations in plasma triglyceride levels. Significant increases in urinary volume were observed in males of the high dose group.

Forty-eight beagle dogs (24 per sex) were randomly assigned to 4 groups of 6 animals/sex/ group. Nilutamide was administered orally at dosage levels of 0, 3, 6 and 12 mg/kg/day for 52 consecutive weeks. Eleven (11) animals either died (n=2) or had to be sacrificed (n=9) during the course of the study. Mortality occurred in all active treatment groups but the incidence was greatest in the 12 mg/kg/day group (n=6). Deaths occurred between the fifth and the eleventh month of treatment. Clinical signs of toxicity were dehydration and pallor of the mucous membranes which appeared at about the ninth month and was not dose-related but which was observed with a greater intensity in the animals sacrificed or found dead during the study. Findings in cases of deaths also revealed anemia accompanied by moderate to marked increases in reticulocyte and platelet counts, fibrinogen level and erythrocyte sedimentation rate and, in some cases, vacuolisation and hypertrophy of hepatocytes. In animals which died during the study, practically all blood biochemistry parameters were impaired. These various toxicities were attributed to chronic anorexia and poor physical condition. No ophthalmologic drug-related effects were noted. A significant dose-related reduction in prostate weights was observed in all treated males. Microscopic pathology revealed atrophy of the tubulo-alveolar units of the prostate in all treated males and inhibition of spermatogenesis in some males of all treated groups. Hematology investigations showed anemia (reductions in mean RBC count, hemoglobin and packed cell volume) in some males of all treated groups but this did not appear to be dose-related. An increase in platelet count was also observed. A significant decrease in serum potassium was seen in males of the mid and high dose groups. At the end of the study, surviving male animals in the 12 mg/kg/day group showed increases in chloride, glucose, cholesterol, total proteins, alpha and gamma globulin and alkaline phosphatase. They also had decreases in calcium, urea and haptoglobin levels. A significant increase in urinary volume was observed in both sexes at the two higher dose levels.

Mutagenicity

No evidence of mutagenicity was observed in gene mutation tests, chromosomic aberration tests and unscheduled DNA synthesis tests.

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