

PRODUCT INFORMATION

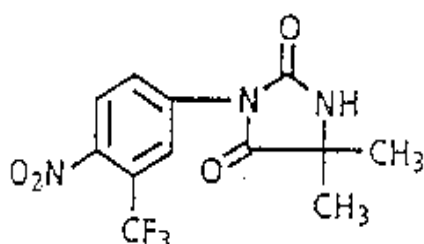
ANANDRON®

NAME OF THE MEDICINE

Non-proprietary name

Nilutamide

Chemical structure



DESCRIPTION

Nilutamide is a non-steroidal orally-active specific antiandrogen. The compound is a white to off-white powder with the chemical name of 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione (MW = 317.2, CAS 63612-50-0).

Each ANANDRON tablet contains nilutamide 150 mg as active ingredient. The tablets also contain lactose, maize starch, povidone, sodium docusate, magnesium stearate and talc as excipients.

PHARMACOLOGY

Pharmacodynamics

As growth and differentiation of prostate cancer cells are dependent on the presence of adequate concentrations of circulating androgens of testicular and adrenal origin, the primary goal in the systemic treatment of metastatic prostate cancer is the suppression and/or blockade of androgenic stimulation.

Nilutamide is not a cytotoxic drug. Nilutamide acts by competing at the level of the prostatic androgen receptor for binding of endogenous steroids and by inhibiting androgen uptake. Nilutamide interacts only with the androgen receptor and not with other steroid hormone receptors (oestrogen, progestin, mineralo- or gluco-corticoid), hence it lacks other hormonal or antihormonal activities.

In addition to antagonising the effects of androgens on prostate tissue, nilutamide also acts at other sites which have androgen receptors including the hypothalamus and pituitary. By interrupting the negative feedback of androgens at the hypothalamo-pituitary level, nilutamide induces a secondary increase in gonadotropin and androgen secretion which overcomes part of the blocking effect. It is therefore advisable to inhibit testosterone secretion by either surgical or medical castration. Combining nilutamide with surgical (bilateral orchidectomy) or chemical (LHRH agonist) castration provides a more complete androgenic blockade than castration alone by counteracting the effects of androgens of adrenal origin which are not affected by any means of castration.

There is considerable debate regarding the relative merits of combination versus monotherapy in advanced prostate cancer, summarised by Dalesio et al 1995 (1) in a meta-analysis of trials of maximal androgen blockade (MAB) involving nilutamide, flutamide or cyproterone acetate in combination with surgical or medical castration. While this analysis did not exclude the possibility of a moderate improvement in survival, there was no statistically significant reduction in the annual odds of death in favour of MAB based on the available data. The meta-analysis included the effect of MAB only on mortality, and did not measure other end-points such as time to disease progression.

Nilutamide prevents the disease flare associated with the administration of an LHRH agonist.

In patients with metastatic prostate cancer who received either nilutamide 300 mg/day with an LHRH agonist or placebo with an LHRH agonist, the nilutamide group achieved chemical castration faster and there was significant prevention of the flare phenomenon, decreased serum prostatic acid phosphatase (PAP) and decreased prostate specific antigen (PSA).

Pharmacokinetics

Absorption

In healthy volunteers, nilutamide was rapidly absorbed following administration of a single oral dose of 100 to 300 mg. The C_{max} (0.8-2.3 mg/L) was reached with a T_{max} of about 2 hours (range 1.5 to 3.1 hours). Results obtained in patients receiving 150 mg/day show a slightly longer T_{max} (2.8 hours) and lower C_{max} (0.9 mg/L) and AUC, but the differences are not considered to be significant.

Analysis of blood, urine and faeces samples following a single oral 150 mg dose of [¹⁴C]-nilutamide in patients with metastatic prostate cancer showed that the drug is rapidly and apparently virtually completely absorbed and that it yields high and persistent plasma concentrations. During repeat dose treatment of patients, the mean steady state plasma concentration is 6-7 mg/L for a 300 mg daily dose, and 3-4 mg/L for a 150 mg daily dose. As expected, given the long half-life of nilutamide (56 hours), steady state is achieved by day 14 (on average). The mean plasma concentration is proportional to the dose administered and is unrelated to serum creatinine levels or to the number of daily doses. Studies of one year duration have shown that there is no accumulation with long term treatment.

Distribution

At concentrations between 0.32 and 32.1 mg/L, binding of nilutamide to plasma proteins is 80-84% and non-saturable. In whole blood, nilutamide is 36% bound to erythrocytes. Binding to plasma proteins and erythrocytes is constant over the range of therapeutic concentrations observed in patients. These results do not indicate any effects that would cause non-linear pharmacokinetics.

Metabolism and excretion

The elimination half-life of nilutamide in patients is 56 hours and in healthy volunteers is 43 hours. The half-life of the metabolites is longer (55-126 hours). Nilutamide is almost completely metabolised and the metabolites are primarily excreted into urine as glucuronide and sulfate conjugates. Renal and faecal excretion of the active drug are negligible. Of the 5 metabolites that have been identified, the main four are amino and hydroxymethyl derivatives of nilutamide. Compared to its metabolites, nilutamide shows higher activity and higher plasma concentrations and is thus the main therapeutic agent.

There is no evidence that renal impairment with elevated serum creatinine levels (150-600 µmol) affects the pharmacokinetics of nilutamide.

CLINICAL TRIALS

Evaluated clinical studies include eight randomised trials combining surgical orchidectomy with nilutamide or placebo and three with LHRH agonists and nilutamide or placebo. The two primary studies involving 457 patients randomised to surgical orchidectomy and nilutamide or placebo and 411 patients randomised to LHRH agonist leuprolide and nilutamide or placebo provide the most pertinent data. Both studies demonstrated that patients receiving nilutamide in combination with surgical or medical castration obtain a higher proportion of objective disease regressions, a significant decrease in the incidence of metastatic related pain and related use of analgesia and, particularly in the case of administration of nilutamide in conjunction with LHRH agonists, inhibition of the "flare phenomenon". Other potential beneficial effects, however, were inconclusive. While there was a longer progression-free survival in patients treated with nilutamide in combination with surgical orchidectomy in one of the primary studies, it was not demonstrated in other evaluated studies. None of the evaluated studies demonstrated a significant improvement in either cancer related or overall survival. A meta analysis of 1191 patients undertaken of the randomised phase III trials comparing surgical orchidectomy with nilutamide or placebo demonstrated similar results, however there was a significant benefit for nilutamide in terms of time to disease progression.

INDICATIONS

ANANDRON is indicated for the treatment of previously untreated metastatic prostatic carcinoma, in conjunction with surgical or medical castration.

ANANDRON prevents the disease flare associated with the use of LHRH agonists.

CONTRAINDICATIONS

ANANDRON is contraindicated in the following patients:

- Patients who are hypersensitive to nilutamide or any excipient
- Patients with severe hepatic impairment
- Patients with severe respiratory insufficiency
- Women
- Children
- Patients who have failed to respond to previous hormonal treatment of the cancer

PRECAUTIONS

The hepatic and respiratory condition of the patient should be checked prior to starting treatment (see **CONTRAINDICATIONS**). Patients should be advised to promptly report any respiratory symptoms or symptoms suggestive of liver injury which develop during treatment.

In patients with pre-existing respiratory insufficiency, treatment should be interrupted and radiological investigations conducted immediately if any worsening of the degree of dyspnoea occurs.

If any patient develops dyspnoea during treatment, administration of nilutamide should be interrupted and a chest X-ray taken. If the results of the X-ray confirm interstitial pneumonitis, then the treatment should be discontinued and corticosteroid therapy considered in patients with severely impaired gas exchange. Immediate referral to a respiratory unit for investigation and treatment is required for patients experiencing acute respiratory insufficiency.

If clinical signs indicative of hepatitis develop (e.g. nausea, vomiting, abdominal pain, jaundice), transaminase levels (ASAT, ALAT) should be determined. If the transaminase levels are more than three times the upper normal limit, treatment should be discontinued.

Patients should be advised not to interrupt their treatment without medical consultation.

Special populations

In the two main pivotal studies, the breakdown of patients according to ethnic origin was: 737 caucasian, 95 black, 29 hispanic, 5 asian. In a small uncontrolled pilot study conducted in Japan, a higher incidence of interstitial pneumonitis (8 of 47 patients) was reported than in controlled trials conducted elsewhere. Consequently, caution should be exercised when treating patients of this ethnic origin.

Antiandrogen withdrawal syndrome

In patients treated with an antiandrogen who have disease progression, discontinuation of the antiandrogen may be associated with a withdrawal response. In a subset of patients, discontinuation of antiandrogen treatment decreases PSA values and improves the clinical condition; however the precise mechanism is not clear and it is not known if this translates into prolonged survival.

Effects on fertility

Degeneration of testicular germinal epithelium was seen in rats given oral doses of nilutamide at a dose of 10 mg/kg/day for 13 weeks and 5 mg/kg/day for 78 weeks. In addition, in a reproductive study, male rats dosed at 25 mg/kg/day or higher for 30 days and mated to normal females exhibited a reduction in the number of implantations and increased resorptions.

Use in pregnancy and lactation

Nilutamide is indicated for male patients only. There are insufficient animal toxicity data to indicate potential risks, and the safety of nilutamide in pregnant or lactating women has not been established. Therefore, nilutamide should not be taken during pregnancy or by nursing mothers.

Carcinogenicity

No animal carcinogenicity studies have been carried out with nilutamide. However, a 78 week dietary study in rats showed dose-related interstitial cell hyperplasia at all dose levels (from 5 mg/kg/day) and an increased incidence of interstitial cell adenoma of the testis at 45 mg/kg/day. *In vitro* and *in vivo* genotoxicity studies, performed with maximum attainable concentrations and dose levels, were negative.

Carcinogenicity studies with two related anti-androgenic drugs in rats have shown an increased incidence of interstitial cell adenomas. This is due to a sustained elevation of LH levels in these animals consequent to the blockade by the anti-androgen of the testosterone mediated feedback on LH levels.

Interactions with other medicines

Due to the effect of nilutamide on certain microsomal enzyme mechanisms, it may reduce the hepatic metabolism of some substances (eg. oral anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, theophylline) thereby delaying their elimination and increasing blood levels. The dosage of these medicines or others with a similar metabolic pathway may require adjustment if taken with nilutamide.

When an oral anticoagulant is administered concomitantly with nilutamide, blood coagulation tests should be monitored (prothrombin time, INR). The dose of the oral anticoagulant should be adjusted if necessary.

Nilutamide may cause alcohol intolerance in some patients resulting in malaise and vasomotor flushes. In such cases, alcohol should be avoided during treatment.

Effect on ability to drive and use machines

No specific studies have been performed to evaluate the effects of nilutamide on driving performance or the ability to operate machinery. Patients who experience visual disorders should refrain from driving until their eyesight has accommodated to the darkness and should avoid driving at night or through tunnels (see **ADVERSE EFFECTS, Visual**). In case of alcohol intolerance, patients should avoid alcohol before driving or operating machinery.

Adverse effects ANANDRON was generally well tolerated by 2,000 patients (including elderly men) treated for periods of up to several years in clinical trials. The most common adverse events (especially nausea, alcohol intolerance, impairment of dark or light adaptation and dizziness) occur early in the course of treatment and usually lessen after one month following dose reduction. The risk of rare but more severe adverse effects may be lessened by careful monitoring.

The following adverse events may be observed during treatment with nilutamide:

Visual

Impaired adaptation to darkness affects approximately 25% of treated patients. Symptoms are generally moderate in intensity and may decrease or disappear on continuation of treatment. The problem may be alleviated by wearing tinted glasses (eg. sunglasses) and is completely reversible following discontinuation of treatment. Treatment discontinuation due to this reaction occurs in only 1 to 2% of patients.

Respiratory

Interstitial pneumonitis affects approximately 1 to 2% of treated patients and generally presents as progressive dyspnoea and possibly coughing, chest pain and/or fever usually within the first three months of therapy. Patients presenting with these symptoms should have nilutamide therapy interrupted and a chest X ray taken to confirm interstitial or alveolo-interstitial changes. Very rarely, the pneumonitis may present as acute respiratory insufficiency, or there may be a progression to this condition if nilutamide treatment is not interrupted at the onset of symptoms. The symptoms usually regress following early discontinuation of treatment with or without corticosteroid therapy.

Hepatic

An increase in transaminases (ALAT, ASAT) has been observed in about 8% of patients treated with nilutamide. This may normalise even on continuing treatment. If the increase exceeds by three fold the upper limit of the normal range, treatment with nilutamide must be stopped. Hepatitis has been reported as an uncommon reaction (see **PRECAUTIONS**). Rare cases of mixed, hepatocellular and fulminant hepatitis have been reported.

Gastrointestinal

Nausea with or without vomiting has been reported with an incidence of 10-23%, however patients taking the maintenance dosage of 150 mg per day are usually free of these symptoms. Nilutamide does not cause diarrhoea.

Endocrine

Impotence, decrease in libido, hot flushes, body hair loss, sweating and gynaecomastia have been reported as common or very common reactions that are related to the therapeutic effect of nilutamide and also to medical or surgical castration.

Haematological

In rare cases, aplastic anaemia has been reported. The relationship to nilutamide has not been established.

Other

Alcohol intolerance (malaise with vasomotor flushes) has been reported with an incidence of 4-10%.

DOSAGE AND ADMINISTRATION

ANANDRON tablets are taken orally as either a once daily dose or as divided daily doses. To achieve maximum benefits, treatment should begin on the day of medical castration (eg. using an LHRH agonist) or surgical castration and continue without interruption.

The following dosages are recommended, irrespective of renal function:

Initial treatment

The dosage for the first four weeks of treatment is **300 mg per day** administered either as a once daily dose or as divided doses (eg. 150 mg twice daily). After four weeks, maintenance treatment should be commenced (see below). Maintenance treatment may be commenced earlier if undesirable effects, especially vomiting or visual effects, occur.

Maintenance treatment

Immediately following four weeks of initial treatment, the dosage is reduced to 150 mg per day administered as a once daily dose.

OVERDOSAGE

Doses in excess of 300 mg/day may result in undesirable effects such as digestive disorders (nausea and vomiting) and/or vertigo which resolve on stopping or reducing the dose.

In case of overdose, steps should be taken to minimise the absorption of nilutamide (eg. oral administration of activated charcoal). If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated. As nilutamide is 80-84% protein bound, dialysis may not be of benefit.

PRESENTATION AND STORAGE CONDITIONS

150 mg tablets (off-white, marked with 168D and company logo RU on reverse): 30 tablets in a blister pack. Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA approval: 23 January 1997
Date of most recent amendment: 14 July 2008

References

(1) Prostate Cancer Trialists' Collaboration Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Lancet 1995; 346: 265-269