PRODUCT MONOGRAPH

PrFLUTAMIDE

Flutamide 250 mg tablets

Non-Steroidal Antiandrogen

Schering-Plough Canada Inc.
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DATE OF PREPARATION:
January 8, 2008

Control # 119107

NAME OF DRUG

FLUTAMIDE

THERAPEUTIC CLASSIFICATION

Non-steroidal antiandrogen

ACTION

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

INDICATIONS AND CLINICAL USE

FLUTAMIDE tablets are indicated for use in combination with LHRH agonistic analogues (such as leuprolide acetate) for the treatment of metastatic prostatic carcinoma (stage D_2). To achieve the benefit of the adjunctive therapy with **FLUTAMIDE**, treatment must be started simultaneously using both drugs. **FLUTAMIDE** Tablets are also indicated as an adjunctive therapy to orchiectomy, in order to achieve complete androgen blockade.

CONTRAINDICATIONS

FLUTAMIDE is contraindicated in patients who have shown hypersensitivity to flutamide or any component of this preparation.

WARNINGS

Gynecomastia occurred in 9% of patients receiving flutamide together with medical castration. Physicians must familiarize themselves with the proper use of LHRH before combination medication is comtemplated.

FLUTAMIDE may cause fetal harm when administered to a pregnant woman. There was decreased 24-hour survival in the offspring of rats treated with flutamide at doses of 30, 100, or 200 mg/kg/day (approximately 3, 9, and 19 times the human dose) during pregnancy. A slight increase in minor variations in the development of the sternebra and vertebra was seen in fetuses of rats at the two higher doses. Feminization of the males also occurred at the two higher dose levels. There was a decreased survival rate in the offspring of rabbits receiving the highest dose (15 mg/kg/day; equal to 1.4 times the human dose).

PRECAUTIONS

Periodic liver function tests and sperm count determinations must be performed in patients on long-term treatment with flutamide.

Since flutamide tends to elevate plasma testosterone and estradiol levels, fluid retention may occur. Accordingly, flutamide should be used with caution in those patients with cardiac disease.
Hepatic Injury: Since transaminase abnormalities, cholestatic jaundice, hepatic necrosis and hepatic encephalopathy have been reported with the use of flutamide, periodic liver function tests should be considered. Appropriate laboratory testing should be done at the first symptom/sign of liver disfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms). If the patient has laboratory evidence of liver injury or jaundice, in the absence of biopsy-confirmed liver metastases, flutamide therapy should be discontinued or the dosage reduced. The hepatic injury is usually reversible after discontinuation of therapy and in some patients, after dosage reduction. However, there have been reports of death following severe hepatic injury associated with the use of flutamide.

Drug interactions: In patients receiving long-term warfarin therapy, increases in prothrombin time have been reported after flutamide monotherapy was initiated. Adjustment of the anticoagulant dose may be necessary when flutamide tablets are administered concomitantly with warfarin.

Information for Patients: Patients should be informed that FLUTAMIDE and the drug used for medical castration should be administered concomitantly, and that they should not interrupt their dosing or stop taking these medications without consulting their physician.

ADVERSE REACTIONS

The most frequently reported adverse reactions to FLUTAMIDE Tablets monotherapy are gynecomastia and/or breast tenderness, sometimes accompanied by galactorrhea. These reactions disappear upon discontinuation of treatment or reduction in dosage. The incidence of gynecomastia is reduced greatly when FLUTAMIDE Tablets are administered concomitantly with an LHRH agonist.

The most frequently reported (greater than 5%) adverse experiences during treatment with FLUTAMIDE in combination with a LHRH agonist are listed in the table below. For comparison, adverse experiences seen with a LHRH agonist and placebo are also listed in the following table.

	(n=294) Flutamide + LHRH-agonist % All	(n=285) Placebo + LHRH-agonist % All
Hot Flashes	61	57
Loss of Libido	36	31
Impotence	33	29
Diarrhoea	12	4
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other GI	6	4

As shown in the table; for both treatment groups, the most frequently occurring adverse experiences (hot flashes, impotence, loss of libido) were those known to be associated with low serum androgen levels and known to occur with LHRH-agonists alone.

The only notable difference was the higher incidence of diarrhoea in the flutamide + LHRH-agonist opposed to the placebo + LHRH-agonist (4%), which was severe in less than 1%.
In addition, the following adverse reactions were reported during treatment with flutamide +LHRH-agonist. No causal relatedness of these reactions to drug treatment has been made, and some of the adverse experiences reported are those that commonly occur in elderly patients.

Cardiovascular System: hypertension in 1% of patients. Rarely thrombophlebitis, pulmonary embolism, myocardial infarction.

Central Nervous System: CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients. Rarely insomnia, tiredness, headache, weakness, blurred vision and decreased libido have been reported.

Endocrine System: gynecomastia in 9% of patients. Rarely breast tenderness sometimes accompanied by galactorrhea.

Gastrointestinal System: nausea/vomiting occurred in 11%; diarrhoea 12%, anorexia 4%, and other GI disorders occurred in 6% of patients. Increased appetite, indigestion and constipation have also been reported.

Hematopoietic System: anaemia occurred in 6% of patients, leukopenia 3%, thrombocytopenia 1%.

Liver and Biliary System: clinically evident hepatitis and jaundice occurred in <1% of patients.

Skin: irritation at the injection site and rash occurred in 3% of patients. Photosensitivity reactions have been reported in five patients.

Other: Pruritus, ecchymosis, herpes zoster, thirst, lymphaedema, lupus-like syndrome, hematuria, reduced sperm counts have been reported rarely in long-term treatment. Edema occurred in 4% of patients; neuromuscular, genitourinary symptoms occurred in 2% of patients. Pulmonary symptoms occurred in <1% of patients.

Laboratory Values: Abnormal laboratory test results reported include elevated SGOT (AST), SGPT (ALT); elevated blood urea nitrogen (BUN) and bilirubin levels; less frequently, elevated serum creatinine levels and elevated gamma-glutamyl transferase levels have been reported.

In addition, the following adverse experiences have been reported during world-wide marketing of FLUTAMIDE Tablets: hemolytic anemia, macrocytic anemia, methemoglobinemia, photosensitivity reactions -- including erythema, ulcerations, bullous eruptions, and epidermal necrolysis -- and change in urine color to an amber or yellow-green appearance, which can be attributed to flutamide and/or its metabolites. Also observed were cholestatic jaundice, hepatic encephalopathy and hepatic necrosis. The hepatic conditions were usually reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with use of flutamide.

DRUG INTERACTIONS

In patients receiving long-term warfarin therapy, increases in prothrombin time have been reported after flutamide monotherapy was initiated. Adjustment of the anticoagulant dose may be necessary when FLUTAMIDE Tablets are administered concomitantly with warfarin.

SYMPTOMS AND TREATMENT OF OVERDOSE

In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquillization, and emesis.

Clinical trials have been conducted with flutamide in doses up to 1500 mg per day for periods up to 36 weeks with no serious adverse effects reported. Those adverse reactions reported included gynecomastia, breast tenderness and some increases in SGOT. The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established.

Since FLUTAMIDE is highly protein bound, dialysis may not be of any use 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.

DOSAGE AND ADMINISTRATION

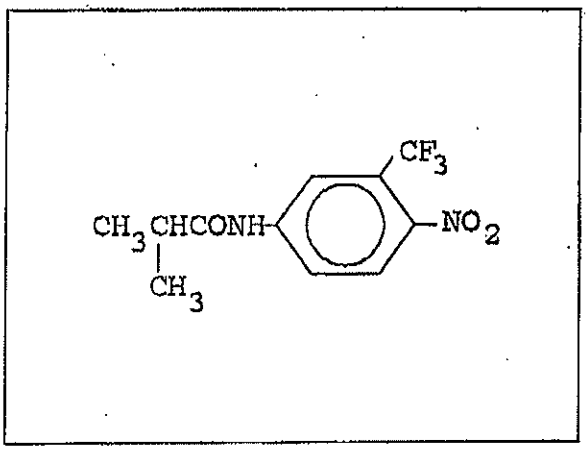
The recommended dose is one 250 mg tablet three times per day.

AVAILABILITY

FLUTAMIDE is available as 250 mg round, pale yellow coloured compressed scored tablets, in bottle of 100 tablets.

CHEMISTRY

Flutamide:



Molecular Formula: $C_{11}H_{11}N_2O_3F_3$ Molecular Weight: 276.21

Chemical Name: 2-methyl-N-(4-nitro-3-(trifluoromethyl) phenyl) propanamide.

Description: Buff to yellow powder.

PHARMACOLOGY

General: In animal studies, flutamide demonstrates potent antiandrogenic effects. It exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues or both. Prostatic carcinoma is known to be androgen-sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen, e.g. castration.

PHARMACOKINETICS

Analysis of plasma, urine, and faeces following a single oral 200 mg dose of tritium-labelled flutamide to human volunteers showed that the drug is rapidly and completely absorbed. It is excreted mainly in the urine with only 4.2% of the dose excreted in the faeces over 71 hours. The composition of plasma radioactivity showed that flutamide is rapidly and extensively metabolized, with flutamide comprising only 2.5% of plasma radioactivity one hour after administration. At least six metabolites have been identified in plasma. The major plasma metabolite is a biologically active alpha-hydroxylated derivative which accounts for 23% of the plasma tritium one hour after drug administration.

The major urinary metabolite is 2-amino-5-nitro-4-(trifluoromethyl)phenol.

Following a single 250 mg oral dose to normal adult volunteers, low plasma levels of varying amounts of flutamide were detected. The biologically active alpha-hydroxylated metabolite reaches maximum plasma levels in about two hours, indicating that it is rapidly formed from flutamide. The plasma half-life for this metabolite is about 6 hours.

Following multiple oral dosing of 250 mg t.i.d. in normal geriatric volunteers, flutamide and its active metabolite approached steady-state plasma levels (based on pharmacokinetic simulations) after the fourth flutamide dose. The half-life of the active metabolite in geriatric volunteers after a single flutamide dose is about 8 hours and at steady-state is 9.6 hours.

Flutamide, *in vivo*, at steady-state plasma concentrations of 24 to 78 ng/mL is 94% to 96% bound to plasma proteins. The active metabolite of flutamide, *in vivo*, at steady-state plasma concentrations of 1556 to 2284 ng/mL, is 92% to 94% bound to plasma proteins.

In male rats neither flutamide nor any of its metabolites are preferentially accumulated in any tissue except the prostate after an oral 5 mg/kg dose of ^{14}C-flutamide. Total drug levels were highest 6 hours after drug administration in all tissues. Levels declined at roughly similar rates to low levels at 18 hours. The major metabolite was present at higher concentrations than flutamide in all tissues studied.

Elevations of plasma testosterone and estradiol levels have been noted following flutamide administration.

Clinical Studies: Flutamide has been demonstrated to interfere with testosterone at the cellular level. This can complement medical castration achieved with leuprolide, which suppresses testicular androgen production by inhibiting luteinizing hormone secretion.

To study the effects of combination therapy, 617 patients (311 leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostatic carcinoma were enroled in a large multicentered, controlled clinical trial.

Three and one-half years after the study was initiated, median survival had been reached. The median actuarial survival times is 34.9 months for patients treated with leuprolide and flutamide versus 27.9 months for patients treated with leuprolide alone. This seven month increment represents 25% improvement in overall survival with the flutamide therapy. Analysis of progression free survival showed a 2.6 month improvement in patients who received leuprolide plus flutamide, a 19% increment over leuprolide and placebo.

TOXICOLOGY

Signs of flutamide overdose were hypoactivity, piloerection, slow respiration, ataxia and/or lacrimation as seen in rat, mouse and guinea pig. Anorexia, tranquillization and emesis were observed in the cat and dog. The oral LD_{50} was in excess of 1000 mg/kg in the cat and dog.

A 52-week chronic oral toxicity study in male and female rats produced a dose-related decrease in body weight gain. Necropsy revealed the following drug-related changes: reduction in prostatic, seminal vesicle and male kidney size; a reduction in testicular or uterine size in the highest dosage groups (18 times human dose); increase in liver size, unusually textured and colored testes, and in females suppression of lactation. Histological drug-related changes in males included testicular interstitial cell hyperplasia, interstitial space edema, and at 52 weeks only, interstitial cell adenoma, spermatogenesis suppression, seminal vesicle and prostatic atrophy and an increase in the number of pituitary castration cells. The adenoma was related to the mechanism of action of flutamide and was species specific.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity studies were performed with flutamide. However, daily administration of flutamide to rats for 52 weeks at doses of 30, 90, or 180 mg/kg/day (approximately 3, 8, or 17 times the human dose), produced testicular interstitial cell adenomas at all doses.

Flutamide did not demonstrate DNA modifying activity in the Ames *Salmonella*/microsome Mutagenesis Assay. Dominant lethal tests in rats were negative.

Reduced sperm counts were observed during a six-week study of flutamide monotherapy in normal volunteers. Flutamide did not affect estrous cycles or interfere with the mating behaviour of male and female rats when the drug was administered at 25 and 75 mg/kg/day prior to mating. Males treated with 150 mg/kg/day (30 times the minimum effective antiandrogenic dose) failed to mate; mating behaviour returned to normal after dosing was stopped. Conception rates were decreased in all dosing groups. Suppression of spermatogenesis was observed in rats dosed for 52 weeks at approximately 3, 8, or 17 times the human dose and in dogs dosed for 78 weeks at 1.4, 2.3, and 3.7 times the human dose.

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