PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr FLUTAMIDE

Flutamide

Tablets, 250 mg, oral

House Standard

ATC index: L02BB01

Non-Steroidal Antiandrogen

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RECENT MAJOR LABEL CHANGES

None	N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUTAMIDE (flutamide) is 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.
- As an adjunctive therapy to orchiectomy, in order to achieve complete androgen blockade.
- FLUTAMIDE in combination with LHRH agonists are also indicated prior to and during definitive external beam radiotherapy for patients with bulky locally advanced Stage B_2 and Stage C prostatic carcinoma. See 4 DOSAGE AND ADMINISTRATION.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 8.2 Clinical Trial Adverse Reactions and 10.3 Pharmacokinetics.

2 CONTRAINDICATIONS

FLUTAMIDE (flutamide) is contraindicated in:

- Patients who are hypersensitive to flutamide or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with severe hepatic impairment.

FLUTAMIDE has not been studied in women and is not indicated for this population, particularly for nonserious or nonthreatening conditions.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Adult Dose

The recommended dosage of FLUTAMIDE (flutamide) in combination with orchiectomy or in combination with a LHRH agonist is one 250 mg tablet three times a day at eight-hour intervals. In combination with a LHRH agonist, either the two agents may be initiated

simultaneously, or FLUTAMIDE therapy may be started 24 hours prior to initiation of the LHRH agonist.

In the management of bulky locally advanced Stage B_2 and Stage C prostatic carcinoma, the recommended dosage is one 250 mg tablet, three times a day at eight-hour intervals. FLUTAMIDE should be started simultaneously or 24 hours prior to initiation of the LHRH agonist. Administration of FLUTAMIDE should begin eight weeks prior to external beam radiation therapy and continue through the course of radiation therapy.

Pediatric

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

No special considerations regarding administration.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquillization, emesis and methemoglobinemia. 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. Gastric lavage may be considered. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 250 mg	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake 16%, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

FLUTAMIDE 250 mg: Each round, pale yellow coloured, biconvex, film-coated tablet, scored and engraved FLUT over 250 on one side and APO on the other side, contains flutamide 250 mg.

Available in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

General

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 contemplated.

Carcinogenesis and Mutagenesis

After long-term administration in rats, flutamide produced testicular interstitial cell adenomas and dose-related increases in mammary gland adenomas or carcinomas. The relevance of these findings to humans is unknown. It should be noted that few cases of malignant breast neoplasms have been reported in male patients receiving flutamide; causality has not been established (see 16 NON-CLINICAL TOXICOLOGY).

- ***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 6-8 weeks for a withdrawal response prior to any decision to proceed with other prostate cancer therapy.

Cardiovascular

FLUTAMIDE is indicated for use in combination with an LHRH analogue or orchiectomy. Based on evidence from the published literature, combined androgen blockade with an antiandrogen plus LHRH analogue increases risk of cardiovascular disease (heart attack, cardiac failure, sudden cardiac death) and adversely affects independent cardiovascular risk factors (serum lipoproteins, insulin sensitivity and obesity). Physicians should carefully consider whether the benefits of combined androgen blockade outweigh the potential cardiovascular risk. Assessment of cardiovascular risk factors, monitoring for signs and symptoms suggestive of development of cardiovascular disease, and management according to local clinical practice and guidelines should be considered.

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.

- ***Effect on QT/QTc interval***

FLUTAMIDE is indicated for use in combination with an LHRH analogue or orchiectomy. The potential for QT/QTc prolongation has not been studied with FLUTAMIDE. Combined androgen blockade studies with other anti-androgen plus LHRH analogue or surgical castration have been associated with the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications (see 9.2 Drug Interactions Overview).

Endocrine and Metabolism

A reduction in glucose tolerance and/or glycated hemoglobin (HbAlc) has been observed in males receiving combined androgen blockade. This may manifest as diabetes or loss of glycemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose and/or glycated hemoglobin (HbAlc) in patients receiving FLUTAMIDE in combination with LHRH analogues.

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.

Hepatic/Biliary/Pancreatic

- ***Hepatic Injury***

There have been postmarketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic

failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, hyperbilirubinuria, 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, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

Treatment with flutamide should not be initiated in patients with serum transaminase levels exceeding 2 to 3 times the upper limit of normal. Since transaminase abnormalities, cholestatic jaundice, hepatic necrosis, and hepatic encephalopathy have been reported with the use of flutamide, periodic liver function tests must be performed in all patients.

Appropriate laboratory testing should be done monthly for the first 4 months, and periodically thereafter, and at the first symptom/sign of liver dysfunction (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 if the patient develops jaundice or if the serum transaminase levels rise to 2 to 3 times the upper limit of normal, even in clinically asymptomatic patients.

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.

Monitoring and Laboratory Tests

Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring patients' response.

Anemia has been observed in patients treated with FLUTAMIDE. Hemoglobin levels should be monitored.

Assessment of cardiovascular risk factors, monitoring for signs and symptoms suggestive of development of cardiovascular disease, and management according to local clinical practice and guidelines should be considered. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Serum transaminase levels should be measured prior to starting treatment with flutamide, then monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction.

Consideration should be given to monitoring blood glucose and/or glycated hemoglobin (HbAlc) in patients receiving FLUTAMIDE in combination with LHRH analogues. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

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

Musculoskeletal

- ***Changes in Bone Density***

FLUTAMIDE is indicated for use in combination with an LHRH analogue or orchiectomy. Based on studies conducted in the literature, decreased bone mineral density can be anticipated with long term combined androgen blockade with an anti-androgen plus LHRH analogue. Combined androgen blockade is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal 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, combined androgen blockade may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy is instituted.

Reproductive Health: Female and Male Potential

No data is available on the effects of flutamide on reproductive health in humans.

7.1 Special Populations

7.1.1 Pregnant Women

No studies have been conducted in pregnant women. Therefore, the possibility that FLUTAMIDE may cause fetal harm if administered to a pregnant woman must be considered.

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).

7.1.2 Breast-feeding

No studies have been conducted in lactating women. Therefore, the possibility that FLUTAMIDE may be present in the breast milk of lactating women must be considered.

7.1.3 Pediatrics (< 18 years)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥ 65 years)

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 8.2 Clinical Trial Adverse Reactions and 10.3 Pharmacokinetics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions to flutamide 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 is administered concomitantly with a LHRH agonist.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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.

Table 2 - Adverse reactions with an incidence of ≥ 5%

	Flutamide + LHRH-agonist (n=294)	Placebo + LHRH-agonist (n=285)
	% All	% All
Hot Flashes	61	57
Loss of Libido	36	31
Impotence	33	29
Diarrhea	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, loss of libido, impotence) were those known to be associated with low serum androgen levels and known to occur with LHRH-agonists alone.

The only notable difference between these treatment groups was the higher incidence of diarrhea in the flutamide + LHRH-agonist group (12%; severe in 5%) as compared to the placebo + LHRH-agonist group (4%; were 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, dizziness, weakness, malaise, 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%; diarrhea 12%, anorexia 4%, and other gastro-intestinal disorders occurred in 6% of patients. Increased appetite, indigestion and constipation have also been reported.

Hematopoietic System: Anemia 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, lymphedema, 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. Interstitial lung disease occurred in <1% of patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Laboratory Values: Reported abnormal laboratory test results 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.

8.5 Post-Market Adverse Reactions

In addition, the following adverse experiences have been reported during world-wide marketing of flutamide: hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, photosensitivity reactions- including erythema, ulcerations, bullous eruptions, and epidermal necrolysis - and change in urine colour 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. Cardiac failure, sudden cardiac deaths have been reported. Hyperglycemia and aggravated diabetes mellitus have been reported very rarely.

Two reports of malignant male breast neoplasms in patients being dosed with flutamide have been reported. One involved aggravation of a pre-existing nodule which was first detected three to four months before initiation of flutamide monotherapy in a patient with benign prostatic hypertrophy. After excision, this was diagnosed as a poorly differentiated ductal carcinoma. The other report involved gynecomastia and a nodule noted two and six months respectively, after initiation of flutamide monotherapy for treatment of advanced prostatic carcinoma. Nine months after the initiation of therapy, the nodule was excised and diagnosed as a moderately differentiated invasive ductal tumor staged T4N0M0, G3, no metastases had advanced.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

FLUTAMIDE is indicated for use in combination with an LHRH analogue or orchiectomy. The potential for QT/QTc prolongation has not been studied with flutamide. Since combined androgen blockade prolongs the QTc interval, the concomitant use of FLUTAMIDE 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).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Leuprolide	T	Interactions between flutamide and leuprolide have not occurred.	
Oral anticoagulants	CT	In patients receiving long-term oral anticoagulant therapy, increases in prothrombin time have been reported after flutamide monotherapy was initiated.	Close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when FLUTAMIDE is administered concomitantly.
Theophylline	CT	Cases of increased theophylline plasma concentrations have been reported in patients receiving concomitant theophylline and flutamide tablets. Theophylline is primarily metabolized by CYP 1A2, which is the primary enzyme responsible for the conversion of flutamide to its active agent 2-hydroxyflutamide.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of 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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

Absorption:

Analysis of plasma, urine, and feces following a single oral 200 mg dose of tritium-labelled flutamide to human volunteers showed that the drug is rapidly and completely absorbed.

Distribution:

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.

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.

Metabolism:

The composition of plasma radioactivity showed that flutamide is rapidly and extensively metabolized, with flutamide comprising 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.

Elimination:

Flutamide is excreted mainly in the urine with 4.2% of the dose excreted in the faeces over 72 hours.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** Following multiple oral dosing of 250 mg three times a day 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.
- **Sex:** FLUTAMIDE has not been studied in women and is not indicated for this population, particularly for nonserious or nonthreatening conditions.
- **Pregnancy and Breast-feeding:** No studies have been conducted in pregnant or lactating women. Therefore, the possibility that FLUTAMIDE may cause fetal harm if administered to a pregnant woman or may be present in the breast milk of lactating women must be considered.
- **Hepatic Insufficiency:** FLUTAMIDE is contraindicated in patients with severe hepatic impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Protect from light and excessive moisture.

12 SPECIAL HANDLING INSTRUCTIONS

None

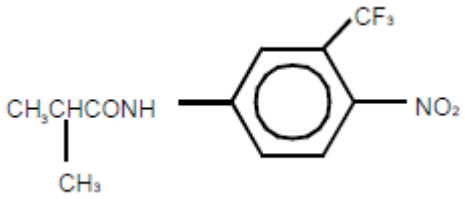
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Flutamide
Chemical name:	1) Propanamide, 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)-phenyl]; 2) α,α,α-Trifluoro-2-methyl-4'-nitro-*m*-propionotoluidide.
Molecular formula and molecular mass:	$C_{11}H_{11}F_3N_2O_3$ and 276.22 g/mol

Structural formula:



Physicochemical properties:

Description:	Pale yellow, crystalline powder.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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.

Combination Therapy: To study the effects of combination therapy, 617 patients (311 different leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostatic carcinoma were enrolled in a large multi-centred, controlled clinical trial.

Three and one–half years after the study was initiated, median survival had been reached. The median actuarial survival times were 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.

Locally Advanced Prostatic Carcinoma: A prospective, multicentre, phase-three trial evaluated the efficacy and safety of the therapy regimen of flutamide and goserelin acetate administered prior to and during definitive external beam radiation therapy to patients with bulky locally

advanced, clinical stage B_2 or C prostate cancer. Patients randomized to the treatment group received flutamide at a dose of 750 mg/day (250 mg three times a day) initiated eight weeks prior to the start of radiation therapy and continued for a total of 16 weeks or until the last day of radiation therapy, whichever occurred first. Flutamide treatment was continued during unexpected interruptions of radiation therapy. These patients also received a depot injection of goserelin acetate 3.6 mg administered subcutaneously into the anterior abdominal wall every four weeks for 16 weeks (total 4 injections) beginning eight weeks prior to initiation of radiation therapy. Patients in the control group were treated with radiation only.

14.2 Study Results

The combination of flutamide and goserelin acetate administered prior to and during radiation therapy increased disease-free survival and loco-regional control without a clinically significant increase in toxicity. Approximately 75% of patients in both groups were alive four years after initial randomization; local failure occurred in 33% of the controls, but in only 16% of the treated patients ($p<0.001$). Over four years, 36% of the controls vs. 27% of the treated patients developed distant metastasis.

When prostate-specific antigen (PSA) levels were not used as a criterion for the presence of disease, duration of disease-free survival was significantly longer in treated patients than in controls ($p<0.001$). Treated patients had an estimated median disease-free survival time of 4.4 years as compared to 2.6 years for control patients. Similarly, when normal PSA levels were considered as part of the survival criteria, treated patients had a significantly longer median disease-free survival time than controls ($p<0.001$). Patients in the treated group had an estimated median disease-free survival period of 2.7 years, while control patients achieved an estimated median disease-free survival time of 1.5 years. It is noteworthy that the increase in disease-free survival time observed among treated patients was achieved with 16 weeks of reversible androgen blockade.

External beam radiation therapy morbidity was not increased by the added combination of flutamide and goserelin acetate. Hot flashes and diarrhea were the most commonly reported adverse events among treated patients (46% and 40%, respectively). Diarrhea also was reported in 40% of the control patients as a late effect of the radiation therapy. Gynecomastia was reported in 3% of the treated patients; elevated SGOT levels were observed in 1% of patients in the treated group. Although more treated patients than controls had abnormal SGOT and/or SGPT levels during the follow-up period, more treated than control patients also had abnormal baseline values as well. During the follow-up period, levels of acid phosphatase were higher in controls than in treated patients.

14.3 Comparative Bioavailability Studies

A randomized, single dose, blinded, two–way crossover comparative bioavailability study, of Flutamide 250 mg tablets (AA Pharma Inc.) versus Euflex® 250 mg tablets (Schering Canada Inc.) was performed in healthy, adult male subjects (n=22) under fasting conditions.

A summary of the results is presented in the following table:

2-Hydroxyflutamide (1 x 250 mg flutamide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (ng*hr/mL)	3016.9 3322.1 (47.9)	3026.0 3201.8 (35.7)	100%	90% – 110%
AUC_I (ng*hr/mL)	3155.8 3463.0 (47.2)	3146.4 3326.0 (35.2)	100%	91% - 111%
C_{max} (ng/mL)	443.2 480.9 (45.5)	555.0 573.4 (27.3)	80%	70% – 91%
T_{max}§ (h)	2.68 (37.97)	2.09 (38.09)		
$t_{1/2}$§ (h)	4.74 (24.73)	4.73 (25.29)		

*Flutamide 250 mg tablets, AA Pharma Inc., Vaughan, Canada

† Euflex® 250 mg tablets, Schering Canada Inc., Purchased in Canada

§Arithmetic mean (%CV) presented only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Signs of flutamide overdose were hypoactivity, piloerection, slow respiration, ataxia and/or lacrimation as seen in the 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 coloured 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.

Carcinogenicity:

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.

In the chronic toxicity studies in male rats, dose - dependent increases in mammary gland adenomas and carcinomas were observed. Both of these findings are related to the recognized mechanism of action of flutamide on endocrine sensitive cells.

Genotoxicity:

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

Reproductive and Developmental Toxicology:

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.

Histologic changes characteristic of the antiandrogenic activity of flutamide were observed in all species, and there was evidence of suppressed spermatogenesis. In rats only, testicular interstitial cell adenomas were increased in number after chronic administration of flutamide independent of the dose administered.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Euflex® (flutamide 250 mg tablets) - Nonsteroidal antiandrogen, submission control Number 157238, Product Monograph. Merck Canada Inc., Kirkland, Quebec. October 15, 2012.
2. Euflex® (flutamide), Schering, Nonsteroidal Antiandrogen. Prescribing Information (CPS Monograph). Compendium of Pharmaceuticals and Specialties, 31st Edition, 1996; pp. 510 - 511.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLUTAMIDE

Flutamide tablets

Read this carefully before you start taking **FLUTAMIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLUTAMIDE**.

What is FLUTAMIDE used for?

FLUTAMIDE, is a treatment for men with some types of prostate cancer. FLUTAMIDE is used in combination with other medicines.

FLUTAMIDE is used together with an injection called "LHRH agonist." This is a combined treatment, called "total androgen blockade". The goal of this treatment is to lower androgen levels and block the effect of androgen on the tumour. The LHRH agonist lowers androgen levels. FLUTAMIDE treatment blocks the effect of androgen on the tumour.

How does FLUTAMIDE work?

Flutamide belongs to a group of medicines called nonsteroidal antiandrogens. It works by blocking the effects of androgen (hormones like testosterone). This helps to stop the growth and spread of cancer cells.

What are the ingredients in FLUTAMIDE?

Medicinal ingredient: Flutamide

Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake 16%, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

FLUTAMIDE comes in the following dosage forms:

Tablet: 250 mg

Do not use FLUTAMIDE if:

- You are allergic to FLUTAMIDE or any other ingredients in FLUTAMIDE.
- You have severe liver problems.
- You are a woman.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUTAMIDE. Talk about any health conditions or problems you may have, including if you:

- have low bone mineral density (BMD).
- have low red blood cell count (anemia).
- have heart disease or have a genetic heart condition called 'long QT syndrome' or family history of this heart condition.
- have diabetes or high blood sugar levels.
- are pregnant.
- are breast feeding.

In addition, you should call your healthcare professional right away if you have any of the following signs or symptoms:

- Itching of the skin
- Loss of appetite
- Nausea and vomiting
- Stomach or abdominal pain
- Fatigue (feeling extremely tired)
- Flu-like symptoms (muscle aches, soreness)
- Brown urine
- Jaundice (yellowing of the skin or whites of the eyes)

Other warnings you should know about:
FLUTAMIDE can cause side effects including:

- **Liver Problems:** Treatment with FLUTAMIDE could cause liver problems. If you have any of the following signs or symptoms, tell your healthcare professional right away:

  - Itching of the skin
  - Loss of appetite
  - Nausea and vomiting
  - Stomach or abdominal pain
  - Feeling extremely tired (fatigue)
  - Muscle aches and soreness
  - Brown urine
  - Yellowing of the skin or whites of the eyes (jaundice)

  Some men taking flutamide therapy have liver damage and needed to be hospitalized. In rare cases, men died because of liver failure while they were taking flutamide tablets. In about half of these cases, the liver failure happened in the first three months that they were taking flutamide tablets.

Because FLUTAMIDE can cause liver failure, you will have regular blood test done to show if you are having liver problems. A recommended schedule for regular blood testing is:

- Before starting FLUTAMIDE
- Every month for the first 4 months of treatment
- Regularly after the first 4 months.

- **Diarrhea:** Diarrhea (2 or more loose or liquid bowel movements in a day) is a common side effect of taking FLUTAMIDE. It can be severe and cause you to be dehydrated, have low blood pressure or kidney problems.

  If you have diarrhea when taking FLUTAMIDE:

  - Drink plenty of fluids
  - Reduce your intake of dairy products (for example, milk, cheese, yogurt)
  - Increase your intake of whole grains, fruits, and vegetables
  - Stop laxative use
  - Take over-the-counter medicine to treat diarrhea

    If your diarrhea continues or it becomes worse, contact your healthcare professional right away.

Check-ups and testing:
You will have regular visits with your healthcare professional during treatment with FLUTAMIDE to monitor your health. They will:

- Check your Prostate Specific Antigen (PSA) levels to ensure your body is responding to treatment.
  - Prostate-specific antigen (PSA) is a marker used for monitoring cancer progression and response to therapy. PSA can be measured from a blood sample.
  - PSA levels are usually higher in cancer progression and lower when responding to treatment.
  - If your PSA levels remain high or increase, your FLUTAMIDE and LHRH agonist treatment will be stopped.
  - Your PSA levels will be monitored for 6 to 8 weeks after stopping treatment to see if they go down.
  - PSA levels will also be monitored to see if other forms of treatment should be considered.
- Do blood tests to check your liver, and blood health.
- Check your heart health.
- Check your bone mineral density.
- Check your blood sugar levels.
- Check your sperm count.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLUTAMIDE:

- Anti-coagulant medication – medicines that prevent blood clots.
- Any medicines that may increase the risk of having an abnormal heartbeat. These could include but are not limited to:
  - Medicines used to treat an abnormal heartbeat (antiarrhythmics) like:
    - quinidine, disopyramide (Class IA)
    - amiodarone, sotalol, dofetilide, ibutilide, dronedarone (Class III)
    - flecainide, propafenone (Class IC)
  - Medicines used to treat psychotic disorders (antipsychotics) like chloropromazine.
  - Medicines used to treat depression (antidepressants) like amitriptyline and nortriptyline.
  - Medicines used to treat pain (opioids) like methadone.
  - Medicines used to treat bacteria infections (antibiotics) like:
    - erythromycin, clarithromycin, azithromycin
    - moxifloxacin
  - Medicines used to treat and prevent malaria infections (antimalarials) like quinine.
  - Medicines that stop the growth of fungi (antifungals).
  - Medicines used to treat nausea and vomiting caused by cancer chemotherapy (5-HT3 receptor antagonists) like ondansetron.
  - Medicines used to treat respiratory diseases (beta-2 adrenoceptor agonists) like salbutamol.
- Drugs containing theophylline– used to treat certain breathing problems.

How to take FLUTAMIDE:

- Always take FLUTAMIDE exactly as your healthcare professional tells you. Check with your healthcare professional if you are not sure.
- You may be getting other treatments in addition to FLUTAMIDE. These could include regular injections of LHRH agonist or radiation therapy.
- FLUTAMIDE and the drug used for medical castration should be taken together, and you should not stop taking these medications without talking to your healthcare professional first.

Usual dose:

Adult Dose:

Take 1 tablet 3 times a day (every 8 hours).

Overdose:

If you think you, or a person you are caring for, have taken too much FLUTAMIDE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of FLUTAMIDE, take it as soon as you remember. Take your next dose at the usual time.

If it is close to the time of your next dose, skip the missed dose. Take your next dose at the usual time.

Do not take two doses at the same time to make up for a missed dose.

What are possible side effects from using FLUTAMIDE?

These are not all the possible side effects you may have when taking FLUTAMIDE. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, loss of appetite (anorexia)
- Diarrhea
- Hot flashes, loss of sex drive (libido), impotence
- Itching, bruising, skin rash, rash or blisters resulting from skin sensitive to strong or long periods of sunlight
- Swelling (lupus-like syndrome)
- Joint or muscle pain
- Thirst
- Difficulty sleeping, tiredness
- Headache, dizziness, weakness, general feeling of being unwell
- Blurred vision
- Increased appetite, indigestion, constipation

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gynecomastia: Breast enlargement in men, breast tenderness.		√	
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness.		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Leukopenia: (decreased white blood cells) – infections, fatigue, fever, aches, pains and flu-like symptoms.		√	
Thrombocytopenia: (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		√	
UNCOMMON			
Hepatitis (Inflammation of liver): Abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin.		√	
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body.		√	
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough.		√	
Mental Status Change: Drowsiness, confusion, depression, anxiety, nervousness		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.		√	
RARE			
Thrombophlebitis: swelling and redness along a vein which is extremely tender or painful when touched.			√
Pulmonary embolism (blood clot in the lung): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath.			√
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			√
Herpes Zoster virus (shingles): a painful skin rash of fluid-filled blisters, blisters appear along a strip of skin, itching.	√		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hematuria (blood in the urine): pink, red or very dark urine.		√	
Oligospermia: reduced sperm counts		√	
Male Breast Cancer: thickening of breast tissue, redness or scaling of skin covering the breast or nipple, discharge from nipple.		√	
VERY RARE			
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue.		√	
FREQUENCY UNKNOWN			
Hemolytic anemia (breakdown of red blood cells): pale skin, feeling tired or weak, dizziness, fainting, thirst, rapid breathing.			√
Macrocytic anemia (a blood disorder in which red blood cells are unusually large; symptoms may include pale skin, shortness of breath, poor concentration, fatigue, loss of appetite and weight).			√
Methemoglobinemia (a blood disorder in which an abnormal amount of methemoglobin is produced; symptoms may include discoloration of skin, headache, difficulty breathing, weakness).			√
Sulfhemoglobinemia (a rare condition in which there is excess sulfhemoglobin in the blood; symptom may include bluish discoloration of skin).			√
Hepatic encephalopathy (a nervous system disorder in which toxins are built up due to improper function of liver affecting brain function).			√
Hepatic necrosis (death of liver cells): abdominal pain and dark urine, fever, light-colored stool, and jaundice (a yellow appearance of the skin and white portion of the eyes).			√
Heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
ability to exercise.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C).

Protect from light and moisture.

Keep out of reach and sight of children.

If you want more information about FLUTAMIDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Product Monograph on the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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