PRODUCT MONOGRAPH

[pr]pms-FLUTAMIDE

Flutamide Tablets

250 mg

Non-steroidal antiandrogen

PHARMASCIENCE INC.
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Montréal, Québec
H4P 2T4

Date of Revision:
December 18, 2012

Submission Control No: 158262

PRODUCT MONOGRAPH

NAME OF DRUG

[pr]pms-FLUTAMIDE
Flutamide Tablets
250 mg

THERAPEUTIC CLASSIFICATION

Non-steroidal antiandrogen

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacokinetics

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

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.

Comparative Bioavailability Studies

A bioavailability study comparing two different formulations of flutamide was performed. Pharmacokinetic and bioavailability data of flutamide and its metabolite, 2-OH flutamide were measured from 30 healthy male volunteers after a single 250 mg oral dose of flutamide was administered. The results can be summarized as follows:

Summary Tables of the Comparative Bioavailability Data of

pms-FLUTAMIDE 250 mg Tablets (Pharmascience Inc., Canada)

versus

EUFLEX 250 mg Tablets (Merck Canada Inc.) 250 mg oral dose administration in the fasting state

Flutamide (1 x 250 mg tablets, Fast) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	22.01 26.62 (58.5)	17.84 24.20 (91.8)	123.4	(95.0-160.2)
AUC_I (ng·h/mL)	29.70 34.44 (59.4)	23.95 32.93 (92.0)	124.0	(93.6-164.2)
C_{max} (ng/mL)	7.26 9.42 (78.2)	7.10 10.20 (114.0)	102.3	(78.2-133.9)
T_{max}§ (h)	1.94 (0.92)	1.52 (0.75)		
$T^{1/2}_{cl}$ € (h)	5.32 (7.28)	6.33 (9.96)		

* pms-FLUTAMIDE, Pharmascience Inc., Montréal, Québec, Canada

† EUFLEX®, Merck Canada Inc.

€the arithmetic means with standard deviation in parenthesis

2-OH Flutamide (1 x 250 mg tablets, Fast) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	3902.85 4102.37 (31.6)	3585.42 3706.56 (26.1)	108.9	(99.4-119.2)
AUC_I (ng·h/mL)	4079.55 4293.28 (32.0)	3751.26 3883.10 (26.4)	108.8	(99.3-119.1)
C_{max} (ng/mL)	604.73 640.79 (34.6)	588.12 618.60 (32.9)	102.8	(91.8-115.2)
T_{max}§ (h)	2.78 (1.04)	2.31 (0.87)		
$T^{1/2}_{cl}$ € (h)	5.11 (1.02)	5.42 (1.25)		

* pms-FLUTAMIDE, Pharmascience Inc., Montréal, Québec, Canada

† EUFLEX®, Merck Canada Inc.

€the arithmetic means with standard deviation in parenthesis

INDICATIONS AND CLINICAL USE

pms-FLUTAMIDE (flutamide) is indicated for use in combination with LHRH (*Luteinizing Hormone Releasing Hormone*) 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 pms-FLUTAMIDE, treatment must be started simultaneously using both drugs. pms-FLUTAMIDE is also indicated as an adjunctive therapy to orchiectomy, in order to achieve complete androgen blockade.

CONTRAINDICATIONS

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

pms-FLUTAMIDE is contraindicated in 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.

WARNINGS

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.

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

pms-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.

Effect on QT/QTc interval

pms-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.

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 pms-FLUTAMIDE in combination with LHRH analogues.

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.

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.

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 pms-FLUTAMIDE in combination with LHRH analogues.

Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

Musculoskeletal

Changes in Bone Density

pms-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.

Use in Pregnancy and Lactation:

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.

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.

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.

Since flutamide tends to elevate plasma testosterone and estradiol levels, fluid retention may occur. Accordingly, pms-FLUTAMIDE should be used with caution in those patients with cardiac disease.

Hepatic Injury:. Treatment with pms-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. pruritis, 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 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 discontinuing 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: Interactions between flutamide and leuprolide have not occurred. In patients receiving long-term oral-anticoagulant therapy, increases in prothrombin time have been reported after flutamide monotherapy was initiated. Therefore close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when flutamide is administered concomitantly.
Cases of increased theophylline plasma concentrations have been reported in patients receiving concomitant theophylline and flutamide. Theophylline is primarily metabolized by CYP 1A2, which is the primary enzyme responsible for the conversion of flutamide to its active agent 2-hydroxyflutamide.

Information for Patients:Patients should be informed prior to initiating this medication, of the possibility of its causing hepatic dysfunction. Instruct the patient to consult the doctor immediately if symptoms of hepatic dysfunction appear. These include itching of the skin, dark urine (amber or yellow-green urine is not a cause of concern), nausea, vomiting, persistent lack of appetite, yellow eyes or skin, tenderness in the right upper abdomen, or “flu-like” symptoms.

pms-FLUTAMIDE (flutamide) is indicated only for use in male patients.

Patients should be informed that pms-FLUTAMIDE and the drug used for medical castration

should be administered concomitantly, and that they should notinterrupt their dosing or stop taking these medications without consulting their physician.

ADVERSE REACTIONS

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 an LHRH agonist.

The most frequently reported (greater than 5%) adverse experiences during treatment with fluatmide 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
Diarrhea	12	4
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other Gastro-ntestinal	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 diarrhoea 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: 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. Interstitial lung disease occurred in < 1% of patients.

Additional Adverse Experiences: In addition, the following adverse experiences have been reported during world-wide marketing of flutamide tablets: hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, 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. Cardiac failure, sudden cardiac death 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.

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

1. **Report online at www.healthcanada.gc.ca/medeffect**
2. **Call toll-free at 1-866-234-2345**
3. **Complete a Canada Vigilance Reporting Form and:**
   - **Fax toll-free to 1-866-678-6789, or**
   - **Mail to: Canada Vigilance Program**
     Health Canada
     Postal Locator 0701E
     Ottawa, Ontario
     K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

DRUG INTERACTIONS

Drug-Drug Interactions

pms-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 pms-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-2adrenoceptor agonists (e.g. salbutamol).

SYMPTOMS AND TREATMENT OF 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 Center immediately.

DOSAGE AND ADMINISTRATION

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

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

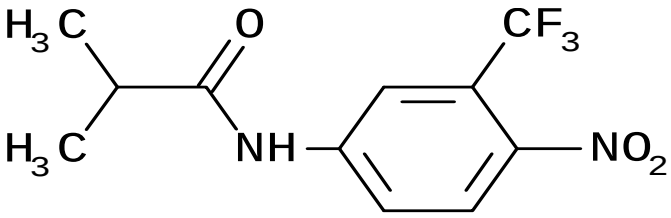
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Flutamide

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

Structural Formula:



Molecular Formula: $C_{11}H_{11}N_20_3F_3$

Molecular Weight: 276.21 g/mol

Description: Flutamide is pale yellow, odorless or almost odorless crystals. The drug is freely soluble in ethanol and acetone. It is soluble in chloroform; practically insoluble in water. Flutamide has a melting point of 111.5°C - 112.5°C.

AVAILABILITY OF DOSAGE FORMS

Each round, biconvex, white-beige to pale yellow tablet debossed *"P" score "250" on* one side and *"FLUTAMIDE"* on the other; contains 250 mg of flutamide as an active ingredient and the folowing nonmedicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, dextrates, dibasic calcium phosphate, lactose, microcrystallinecellulose, sodium lauryl sulfate and stearic acid.

Available in bottles of 100 tablets.

Stability and Storage Recommendations

Store between 15°C and 30°C. Protect from light and excessive moisture.

INFORMATION FOR THE CONSUMER

- Read this information carefully each time your prescription is refilled because there may be new information available.
- This summary does not tell you everything you need to know about pms-FLUTAMIDE (flutamide) therapy. Your doctor is the best source of information about your treatments. Ask your doctor about questions you have.

What is pms-FLUTAMIDE Therapy?

pms-FLUTAMIDE tablet, in combination with other therapies, is a treatment option for men with some types of prostate cancer.

Prostate cancer results from the abnormal growth of prostate cells. Medical scientists do not know exactly what causes the abnormal cells, but age, environment and genetics are important factors. Male hormones ("androgens") cause the cancer to grow. The cancer growth can be slowed down by blocking the effect of androgens.

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 elevated in cancer progression and low when responding to therapy.

pms-FLUTAMIDE is used together with an injection called "LHRH agonist", as a combined treatment, called "total androgen blockade". The goal of this treatment is to reduce androgen levels and to block the effect of androgen on the tumor. The LHRH agonist reduces androgen levels.

pms-FLUTAMIDE therapy blocks the effect of androgen on the tumor.

Who Should Not Take pms-FLUTAMIDE?

You should not take **pms-FLUTAMIDE** tablets if you have liver problems or if you are allergic to it.

Women should not take **pms-FLUTAMIDE** tablets.

Important Risks You Should Know About pms-FLUTAMIDE Therapy

Some men taking flutamide had liver injury 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 occurred in the first 3 months that they were taking flutamide tablets.

Because **pms-FLUTAMIDE** can cause liver failure, it is very important that you have all blood tests recommended by your doctor. These tests help identify whether you are having liver problems. A recommended schedule for these blood tests is:

- before starting **pms-FLUTAMIDE** treatment
- every month for the first 4 months of therapy
- periodically after the first 4 months

BEFORE you use **pms-FLUTAMIDE** talk to your doctor or pharmacist if:

- You have low bone mineral density (BMD).
- You have low red blood cell count (anemia).
- You have heart disease, or have a heart condition called 'long QT syndrome' or family history of this heart condition.
- You have diabetes or elevated blood glucose.

Also, your doctor will be monitoring your PSA blood concentrations during treatment. If PSA values remain high or start to increase, it is likely that your pms-FLUTAMIDE and LHRH agonist treatment will be discontinued. Your PSA values will continue to be monitored for 6 to 8 weeks after discontinuing treatment to see if the PSA values go down, and whether other forms of treatment should be considered.

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

- 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)

How to Take pms-FLUTAMIDE

- Take your **pms-FLUTAMIDE** tablets as your doctor has prescribed.
- Your doctor will determine whether **pms-FLUTAMIDE** therapy is right for you based on many different factors. These include how large your tumor is, how far it has spread, and your physical condition. In addition to **pms-FLUTAMIDE** tablets, you may be getting other treatments including regular injections of LHRH agonist or radiation therapy. Do not stop or interrupt any treatment without consulting your healthcare professional.

- If you miss a dose of **pms-FLUTAMIDE** tablets, simply continue therapy with your next scheduled dose. Do not try to make up for it by taking extra tablets.

Overdose:

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

Taking Other Medicines

If you are taking any other medicines, tell your doctor before beginning **pms-FLUTAMIDE** therapy.

Flutamide is known to interact with anti-coagulant medication, any medicines that may increase the risk of having an abnormal heart rhythm, as well as drugs containing theophylline as an active ingredient.

Other Possible Side Effects of Taking pms-FLUTAMIDE Tablets

In a medical study, when flutamide tablets were taken together with an LHRH agonist, the most common side effects were hot flashes, loss of sex drive (libido), and impotence. In addition, some men had diarrhea, nausea or vomiting, and breast enlargement.

In another medical study, when flutamide was taken together with goserelin acetate (an LHRH agonist) and radiation therapy, the side effects of flutamide were about the same as when radiation therapy was given alone. These included hot flashes, diarrhea, nausea, and skin rash.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

4. Report online at www.healthcanada.gc.ca/medeffect
5. Call toll-free at 1-866-234-2345
6. Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

What to do when you get Diarrhea

If you experience moderate diarrhea due to **pms-FLUTAMIDE** tablets, the following advice may help:

- 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 nonprescription antidiarrheal medicines

If your diarrhea continues or it becomes severe, contact your doctor right away.

Other Laboratory Tests Your Doctor May be Performing

Your doctor may perform other regular tests (such as the PSA [Prostate Specific Antigen] blood test) to ensure that your body is responding to treatment. Ask your doctor if you have any questions about how your **pms-FLUTAMIDE** therapy is being monitored.

Please ask your doctor about any questions concerning prostate cancer or **pms-FLUTAMIDE** therapy, or you can also ask for a more detailed leaflet that is written for healthcare professionals.

How to store pms-FLUTAMIDE?

Keep pms-FLUTAMIDE and all medicines out of the reach of children. Store between 15°C and 30°C. Protect from light and excessive moisture.

More Information

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
Pharmascience Inc.
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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.

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.

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 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: 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.

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. 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.

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