PRODUCT MONOGRAPH

[Pr] TEVA–FLUTAMIDE
(flutamide tablets)

250 mg

Non-Steroidal Antiandrogen

Teva Canada Limited
30 Novopharm Court
Toronto, Canada
M1B 2K9

Date of Revision: December 02, 2014

Control Number: 174585

Pr TEVA–FLUTAMIDE
(flutamide tablets)

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 prostrate 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 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 steadystate 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 14C-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.

A comparative bioavailability study was performed on two 250 mg flutamide products in 12 healthy volunteers. The pharmacokinetic plasma data calculated for the TEVA-FLUTAMIDE and EUFLEX® tablet formulations is tabulated below:

Comparative Bioavailability Studies

Pharmacokinetic Indices for Plasma Hydroxyflutamide:

Flutamide (1 x 250 mg) From measured data Geometric Mean Arithmetic Mean (C.V.)				
	Test**	Reference***	Ratio of Geometric Means (%)	90% Confidence Interval
AUC_{0-T} (ng•h/ml)	4292 4586 (39)	4015 4228 (37)	107	96.63% - 124.77%
AUC_I (ng•h/ml)	4474 4793 (40)	4164 4395 (38)	107	96.20% - 124.54%
C_{max} (ng/ml)	599 627 (32)	649 677 (32)	92	80.05% - 107.35%
T_{max}* (h)	3.33 (1.21)	2.29 (0.99)	—	—
$T_{1/2}$* (h)	7.45 (2.55)	7.65 (3.01)	—	—

*For T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
** Teva-Flutamide 250 mg Tablets (Teva Canada Limited, Canada)
***EUFLEX® manufactured by Schering Canada Inc., Pointe Claire, Quebec, Canada (purchased in canada).

INDICATIONS AND CLINICAL USE

TEVA-FLUTAMIDE (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 TEVA-FLUTAMIDE, treatment must be started simultaneously using both drugs. TEVA-FLUTAMIDE tablets are also indicated as an adjunctive therapy to orchiectomy, in order to achieve complete androgen blockade.

TEVA-FLUTAMIDE tablets 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 Dosage and Administration).

CONTRAINDICATIONS

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

TEVA-FLUTAMIDE (flutamide) is contraindicated in patients with severe hepatic impairment.

TEVA-FLUTAMIDE (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

TEVA-FLUTAMIDE (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

TEVA-FLUTAMIDE (flutamide) is indicated for use in combination with an LHRH analogue or orchiectomy. The potential for QT/QTc prolongation has not been studied with EUFLEX®. 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 TEVA-FLUTAMIDE (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 TEVA-FLUTAMIDE (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 TEVA-FLUTAMIDE (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
TEVA-FLUTAMIDE (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 TEVA-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, flutamide should be used with caution in those patients with cardiac disease.

Hepatic Injury: Treatment with TEVA-FLUTAMIDE (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 perofrmed in all patinets.
Appropriate laboratory testing should be done monthly for the first 4 months, and periodically thereafter and at the first symptom/sign of liver dysfunction (eg. 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 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 use of flutamide.

Drug Interactions: Interactions between flutamide tablets 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 tablets are administered concomitantly.

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.

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.

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

Patients should be informed that TEVA-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 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
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, 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 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 GI 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, lymphoedema, 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 the 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 preexisting 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: 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.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

DRUG INTERACTIONS

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

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, 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 suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

The recommended dosage of TEVA-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 TEVA-FLUTAMIDE tablet 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. TEVA-FLUTAMIDE should be started simultaneously or 24 hours prior to initiation of the LHRH agonist. Administration of TEVA-FLUTAMIDE should begin eight weeks prior to external beam radiation therapy and continue through the course of radiation therapy.

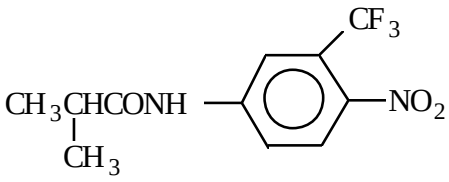
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Flutamide

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

Structural Formula:



Molecular Formula: $C_{11}H_{11}F_3N_2O_3$ Molecular Weight: 276.21

Description: Flutamide is a beige to yellow coloured crystalline powder, soluble in ethanol and acetone and insoluble in water. Melting point is between 110°C and 114°C.

COMPOSITION:

Lactose, pregelatinized starch, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methylcellulose, sodium lauryl sulfate, colloidal silicon dioxide and magnesium stearate.

STABILITY AND STORAGE RECOMMENDATIONS: Store at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

TEVA-FLUTAMIDE (flutamide) is available as light yellow coloured, round, standard convex compressed tablets, engraved modified N|N on one side and 250 on the other side containing 250 mg of flutamide. Supplied in bottles of 100.

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 EUFLEX® (flutamide) therapy. Your doctor is the best source of information about your treatments. Ask your doctor about questions you have.

What is Teva-Flutamide Therapy?

Teva-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.

Teva-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.

Teva-Flutamide therapy blocks the effect of androgen on the tumor.

Who Should Not Take Teva-Flutamide?

You should not take Teva-Flutamide tablets if you have liver problems or if you are allergic to it. Women should not take Teva-Flutamide tablets.

Important Risks You Should Know About Teva-Flutamide Therapy

Some men taking Teva-Flutamide had liver injury and needed to be hospitalized. In rare cases, men died because of liver failure while they were taking Teva-Flutamide tablets. In about half of these cases, the liver failure occurred in the first 3 months that they were taking Teva-Flutamide tablets.

Because Teva-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 Teva-Flutamide treatment
- every month for the first 4 months of therapy
- periodically after the first 4 months

BEFORE you use Teva-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 Teva-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 Teva-Flutamide
- Take your Teva-Flutamide tablets as your doctor has prescribed.
- Your doctor will determine whether Teva-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 Teva-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 Teva-Flutamide tablets, simply continue therapy with your next scheduled dose. Do not try to make up for it by taking extra tablets.

Taking Other Medicines
If you are taking any other medicines, tell your doctor before beginning Teva-Flutamide therapy. Teva-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 Teva-Flutamide Tablets
In a medical study, when Teva-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 Teva-Flutamide was taken together with goserelin acetate (an LHRH agonist) and radiation therapy, the side effects of Teva-Flutamide were about the same as when radiation therapy was given alone. These included hot flashes, diarrhea, nausea, and skin rash.

What to do when you get Diarrhea
If you experience moderate diarrhea due to Teva-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 Teva-Flutamide therapy is being monitored.

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

PHARMACOLOGY

General: In animal studies, flutamide demonstrated 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, eg. 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 leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostatic carcinoma were enrolled 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.

Locally Advanced Prostatic Carcinoma: A prospective, multicenter, 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.

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 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 phophatase were higher in controls than in treated patients.

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 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.

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.

REFERENCES

1. Merck Canada Inc., data on file.

2. Neri R, Florance K, Koziol P, and Van Cleave S: A biological profile of a nonsteroidal antiandrogen, SCH 13521 (4-nitro-3'-trifluoromethyl-isobutyranilide). Endocr 91:427-437, 1972.

3. Peets EA, Henson MF, and Neri R: On the mechanism of the antiandrogenic action of flutamide (α,α,α-trifluoro-2-methyl-4'-nitro-m-propionoto-toluidide) in the rat. Endocr 94:532-540, 1974.

4. Sogani PC, Ray B, and Whitmore WF Jr: Advanced prostatic carcinoma. Flutamide therapy after conventional endocrine treatment. Urology VI:164-166, 1975.

5. Sogani PC and Whitmore WF Jr: Experience with flutamide in previously untreated patients with advanced prostatic cancer. J Urol 122:640-643, 1979.

6. Katchen B and Buxbaum S: Disposition of a new, non-steroid, antiandrogen, α,α,α-trifluoro-2-methyl-4'-nitro-m-propiono-toluide (Flutamide), in men following a single oral 200 mg dose. J Clin Endocrinol Metab 41:373-379, 1975.

7. Airhart RA, Barnett TF, Sullivan JW, Levine RF, and Schlegel JU: Flutamide therapy for carcinoma of the prostate. South Med J 71: 798-801, 1978.

8. Kassem NY, Neri RO, and Munroe JS: Effect of flutamide, an antiandrogen on stage D cancer of the prostate. Clin Pharmacol Ther 29:256 (abstract), 1981.

9. Kassem NY and Neri RO: Flutamide in advanced cancer of the prostate. Clin Pharmacol Ther 31:238 (abstract), 1982.

10. Sogani PC, Vagaiwala MR, Whitmore WF Jr. Experience with flutamide in patients with advanced prostatic cancer without prior endocrine therapy. Cancer 54:744-750, August 15, 1984.

11. Neri R, Kassem N. Biological and clinical properties of antiandrogens. Progress in Cancer Research and Therapy 31: 507-518, 1984.

12. Crawford ED, Dawkins CA. Diagnosis and management of prostate cancer. Hospital Practice 159-171, March 15, 1986.

13. Waxman J. Gonadotrophin hormone releasing analogues open new doors in cancer treatment. Br Med J 295:1962-3, 1987.

14. Peeling WB. A Phase 111 trial comparing ICI118,630 (Zoladex) with orchidectomy in the management of advanced prostatic cancer. In Zoladex - a new treatment for prostatic cancer, edited by GD Chisholm, Royal Society of Medicine Services International Congress and Symposium Series No. 125, Royal Society of Medicine Services Limited, 1987.

15. Labrie F, Dupont A, Giguère M, Borsanyi J-P, Lacourcière Y, Monfette, Emond J, Bergeron N. Benefits of combination therapy with flutamide in patients relapsing after castration. Br J Urol 61:341-346, 1988.

16. Sogani PC and Whitmore WF Jr: Flutamide and other antiandrogens in the treatment of advanced prostatic carcinoma. Osborne CK (ed). Endocrine Therapies in Breast and Prostate Cancer, Martimus Nijhoff Publishers, Boston, pp 131 et seq, 1988.

17. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr A, Blumenstein BA, Davis MA, Goodman PH. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 321: 419-424, 1989.

18. Denis LJ, Carneiro de Moura JL, Bono J, Sylvester R, Whelan P, Newling D, Depauw M. Goserelin acetate and flutamide versus bilateral orchiectomy : A phase III EORTC trial (30853). Urology 1993; 42/2: 119-129.

19. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, Milani RV, Sagalowsky AI, Smith MR, Zakai N; American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation. 2010 Feb 16;121(6):833-40. Epub 2010 Feb 1. PubMed PMID: 20124128

20. Euflex® (flutamide) tablets, Product Monograph, Merck Canada Inc., 16750 route Transcanadienne, Kirkland, Quebec, October 15, 2012, Control # 157238.

21. Pharmacology and toxicology review for Eulexin (flutamide) capsules, NDA 18-554, Schering Corporation, Bloomfield, New Jersey, 1980.

22. A three-way single-dose fasting bioavailability study of flutamide 250 mg tablets in normal healthy non-smoking male volunteers. Completed July, 1994.