EULEXIN®
brand of flutamide
Capsules, USP

WARNINGS
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 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 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, hepatitis, 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.

DESCRIPTION
EULEXIN Capsules contain flutamide, an acylaminotetrazole, orally active androgen antagonist having the chemical name, 2-methyl-4-N-[4-nitro-3-(trifluoromethyl)phenyl]propionamide.

Each capsule contains 125 mg flutamide, USP. The compound is a buff to yellow powder with a molecular weight of 276.2 and the following structural formula.

\[
\begin{align*}
\text{CH} & \text{CHCONH} \\
\text{CH} & \text{3} \\
\end{align*}
\]

The inactive ingredients for EULEXIN Capsules include: corn starch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain bauxite, alcohol, gelatin, colloidal silicon dioxide, dextrose calcium dextrose, methylparaben, propylparaben, and sodium propionate, and the following dyes: FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, titanium dioxide, black ink, and other inactive ingredients.

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

Pharmacokinetics
Absorption: Analysis of plasma, urine, and feces following a single oral 200 mg dose of tritium-labeled flutamide to human volunteers showed that the drug is rapidly and completely absorbed. Following a single 250 mg oral dose to normal adult volunteers, the bioavailability of flutamide is approximately 90%.

Distribution: In male rats administered an oral 5 mg/kg dose of "C-flutamide, neither flutamide nor any of its metabolites is preferentially accumulated in any tissue except the prostate. 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 is present at higher concentrations than flutamide in all tissues studied. Following a single 250 mg oral dose to normal adult volunteers, low plasma concentrations of flutamide were detected. The plasma half-life for the alpha-hydroxylated metabolite should be at least equal to the plasma concentrations of 1556 to 2284 ng/ml at 8 hours, and 540 to 870 ng/ml at 24 hours. Excretion: Flutamide and its metabolites are excreted mainly in the urine with only 4.2% of a single dose excreted in the feces over 72 hours.

PRODUCT INFORMATION

EULEXIN Capsules are indicated for use in combination with LHRH agonists for the management of locally confined Stage B-C and Stage D1 metastatic carcinoma of the prostate.

Stage B-C Prostatic Carcinoma: Treatment with EULEXIN Capsules and the gonadotropin releasing hormone agonist should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Stage D1 Metastatic Carcinoma: To achieve benefit from treatment, EULEXIN Capsules should be initiated with the LHRH-agonist prior to or continued during radiation therapy.

CONTRAINDICATIONS: EULEXIN Capsules are contraindicated in patients who are hypersensitive to flutamide or any component of this preparation.

WARNINGS: EULEXIN Capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be elevated prior to treatment).

INDICATIONS AND USAGE: EULEXIN Capsules are indicated for use in combination with LHRH agonists for the management of locally confined Stage B-C and Stage D1 metastatic carcinoma of the prostate.

Plasma Pharmacokinetics of Flutamide and Hydroxyflutamide in Geriatric Volunteers (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Single Dose</th>
<th>Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>25.2 ± 34.2</td>
<td>113 ± 213</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>8.1 ± 1.3</td>
<td>9.6 ± 3.5</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.9 ± 0.7</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>7.8 ± 1.0</td>
<td>9.6 ± 3.5</td>
</tr>
<tr>
<td>Hydroxyflutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>894 ± 406</td>
<td>1693 ± 586</td>
</tr>
</tbody>
</table>

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

No significant alterations in flutamide administration, distribution, metabolism, or excretion due to race. There have been no significant alterations in flutamide administration, distribution, metabolism, or excretion due to race.

Renal impairment: Following a single 250 mg dose of flutamide administered to subjects with chronic renal insufficiency, there appeared to be no correlation between creatinine clearance and either Cmax or AUC of flutamide. Renal impairment did not have an effect on the Cmax or AUC of the pharmacologically active alpha-hydroxylated metabolite of flutamide. In subjects with creatinine clearance of <29 ml/min, the half-life of the active metabolite was slightly prolonged. Flutamide and its active metabolite were not well distributed. Close adjustment in patients with chronic renal insufficiency is not warranted.

Hepatic impairment: No information on the pharmacokinetics of flutamide in hepatic impairment is available (see BOXED WARNING).

Women: EULEXIN Capsules have not been studied to women or pediatric subjects.

Drug interactions: Interactions between EULEXIN Capsules and LHRH-agonists have not been adequately studied combined with radiation on the cellular level. This can complement medical castration achieved with LHRH-agonists which suppresses testicular androgen production by inhibiting luteinizing hormone secretion.

The effects of combination therapy have been evaluated in two studies. One study evaluated the effects of flutamide and an LHRH-agonist as neoadjuvant therapy to radiation in stage B-C prostate carcinoma and the other study evaluated flutamide and an LHRH-agonist as the sole therapy in stage D1 prostate carcinoma.

Stage B-C Prostatic Carcinoma: The effects of hormonal treatment combined with radiation was studied in 466 patients (251 EULEXIN + gonadotropin implant + radiation, 225 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C1), with or without pelvic node involvement.

In the multicentered, controlled, trial, administration of EULEXIN Capsules (250 mg b.i.d.) and hydroxyflutamide (3.6 mg eqd) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (15% vs 33% at 4 years, P=0.001).

The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, P=0.030).

Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, P=0.001).

Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, P=0.001).

Stage D1 Prostate Carcinoma: To study the effects of combination therapy in metastatic disease, 617 patients (311 leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostate 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 time was 34.9 months for patients treated with leuprolide and flutamide versus 27.9 months for patients treated with leuprolide alone. This 7-month increment represents a 25% improvement in overall survival-time 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.

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Warnings: EULEXIN Capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be elevated prior to treatment).

Indications and Usage: EULEXIN Capsules are for use only in men. This product has no indication for women, and should not be used in this population, particularly for nonsensory or nonlife-threatening conditions.

Fetal Toxicity: Flutamide may cause fetal harm when administered to a pregnant woman (see Pregnancy).
Product Information

Aniline Toxicity: One metabolite of flutamide is 4-nitro-3-fluoroaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia, and chestwall pain, have been observed in both animal and human studies after flutamide administration. None of these toxicities have been observed in patients susceptible to aniline toxicity (e.g., persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease, and smokers). Monitoring of methemoglobin levels should be considered.

PRECAUTIONS: General: In clinical trials, gynecomastia occurred in 9% of patients receiving flutamide together with medical castration.

Information for Patients: Patients should be informed that EULEXIN Capsules 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.

Laboratory Tests: Regular assessment of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patients' response. If PSA levels rise significantly and consistently during EULEXIN therapy the patients should be evaluated for clinical progression. For patients with objective progression of disease together with an elevated PSA, a treatment period free of anti-androgen withdrawal may be considered.

Drug Interactions: Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide was initiated. Therefore, close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when EULEXIN Capsules are administered concomitantly with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 1-year dietary study in male rats, testicular cell adenomas of the testes were present in 49% to 76% of all treated rats (daily doses of 10, 30, and 50 mg/kg/day were administered). These produced plasma Cpg values that were 1- to 2- to 3- and 4-fold, respectively, those associated with therapeutic doses in humans. In male rats similarly dosed for 1 year, tumors were still present after 1 year of a drug-free period, but the incidences were 43% to 47%. In a 2-year carcinogenicity study in male rats, daily administration of flutamide at these same doses produced testicular interstitial cell adenomas in 91% to 95% of all treated rats as opposed to 11% of untreated control rats. Mammary adenomas, adenomatous carcinomas, and fibroadenomas were increased in treated male rats at exposure levels that were 1- to 4-fold those observed during therapeutic dosing in humans. There are no adequate long-term studies in animals treated with EULEXIN Capsules (see ADVERSE REACTIONS section).

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

Reduced sperm counts were observed during a 6-week study of flutamide monotherapy in normal human volunteers.

Flutamide did not affect estrous cycles or interfere with the mating behavior 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 for 60 days had the maximum effective antifertility dose, while females treated to male mating behavior 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 8.8 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.

Animal Toxicology: Serious cardiac lesions were observed in 2/10 beagle dogs receiving 25 mg/kg/day for 16 weeks and 3/10 receiving 40 mg/kg/day for 4 years. These lesions, indicative of chronic injury and repair processes, included chronic myocardial degeneration, intramural fibrosis, myocardial acidophilic degeneration, vascular, and perivascular. The doses at which these lesions occurred were associated with 2-hydroxyflutamide levels that were 1- to 12-fold greater than those observed in humans at therapeutic levels.

Pregnancy: Pregnancy Category D. There was decreased 24-hour survival in the offspring of pregnant rats treated with flutamide at doses of 30, 100, or 200 mg/kg/day (approximately 3, 9, and 19 times the human dose). A slight increase in minor variations in the development of the sphenoid and vertebral was seen in fetuses of rats treated with two higher doses. Neonatal mortality in the male rats 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).

ADVERSE REACTIONS: Stage B, C Prostatic Carcinoma: Treatment with EULEXIN Capsules and the gonadorelin acetate implant did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing flutamide + gonadorelin acetate implant + radiation versus radiation alone. The most frequently reported (greater than 3%) adverse experiences are listed below.

<table>
<thead>
<tr>
<th>Adverse Events During Axile Radiation Therapy (within first 50 days of radiation therapy)</th>
<th>(n=239)</th>
<th>Gonadorelin acetate implant + EULEXIN Radiographs % All % All</th>
<th>Adverse Events During Late Radiation Phase (after 50 days of radiation therapy)</th>
<th>(n=223)</th>
<th>Gonadorelin acetate implant + EULEXIN Radiographs % All % All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>Large Bowel</td>
<td>Bladder</td>
<td>Spleen</td>
<td>Diarrhea</td>
<td>36 40</td>
</tr>
<tr>
<td>80 76</td>
<td>35 60</td>
<td>37 37</td>
<td>36 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>Rectal bleeding</td>
<td>Proctitis</td>
<td>Hematuria</td>
<td>16 18</td>
<td>20 20</td>
</tr>
</tbody>
</table>

Additional adverse event data were collected for the combination therapy with radiation treatment group overall but the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients were: hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

Stage D Metastatic Carcinoma: The following adverse experiences were reported during a randomized trial comparing flutamide + LH-RH agonist versus placebo + LH-RH agonist. The most frequently reported (greater than 5%) adverse experiences during treatment with EULEXIN Capsules in combination with an LH-RH agonist are listed in the following table. For comparison, adverse experiences seen with an LH-RH agonist and placebo are also listed in the following table.

<table>
<thead>
<tr>
<th>(n=294)</th>
<th>Flutamide + LH-RH agonist % All</th>
<th>Placebo + LH-RH agonist % All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes</td>
<td>Loss of libido</td>
<td>Impotence</td>
</tr>
<tr>
<td>61 57</td>
<td>36 31</td>
<td>28 29</td>
</tr>
</tbody>
</table>

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 LH-RH agonists alone.

As the only notable difference was the higher incidence of diarrhea in the flutamide + LH-RH agonist group (12%), which was severe in 5% as opposed to the placebo + LH-RH agonist (4%), which was severe in less than 1%.

In addition, the following adverse reactions were reported during treatment with Flutamide + LH-RH agonist:

Cardiovascular System: hypertension in 1% of patients.

Central Nervous System: CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients.

Gastrointestinal System: anorexia 4%, and other GI disorders occurred in 6% of patients.

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

Liver and Biliary System: hepatitis and jaundice in less than 1% of patients.

Skin: irritation at the injection site and rash occurred in 3% of patients.

Other: edema occurred in 4%, genitourinary and neuromuscular symptoms in 2%, and pulmonary symptoms in less than 1% of patients.

In addition, the following spontaneous adverse experiences have been reported during the marketing of flutamide: hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, protoporphyrinemia, photosensitivity reactions (including erythema, ulceration, bulbar eruptions, and epidermal necrolysis), and urticaria discoloration. The urticaria was noted to change to an amber or yellowgreen appearance which can be attributed to the flutamide and/or its metabolites. Also reported were cholestatic jaundice, hepatic encephalopathy, and hepatic necrosis. The hepatic conditions were often reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with use of flutamide.

Malignant breast neoplasms have occurred rarely in male patients being treated with EULEXIN Capsules.

Extravascular Adenopathy: Incidence of lymphadenopathy was 15% at baseline and 17% at 6 months and 14% at 12 months.

Biopsy: Biopsy of lymph nodes was performed in 15% of patients at baseline and 11% of patients at 6 months and 17% of patients at 12 months. No abnormalities were noted.

OVERDOSAGE: In animal studies with flutamide alone, signs of overdose included hypotension, paresis, and tremor. In clinical studies with flutamide alone or in combination with LH-RH agonists, the most significant symptom was vomiting. No other symptoms were seen in these studies.

DOSE AND ADMINISTRATION: The recommended dosage is 2 capsules 3 times a day at 8-hour intervals for a total daily dose of 750 mg.

HOW SUPPLIED: EULEXIN Capsules. 125 mg, are available as opaque, two-toned brown capsules, imprinted with "Scherger 525". They are supplied as follows:

NDC 0985-0525-05 - Bottles of 500
NDC 0985-0525-05 - Unit Dose packages of 100 (10 x 10s)
NDC 0985-0525-05 - Bottles of 180
Store between 2° and 30°C (36° and 86°F).

Protect the Unit Dose packages from excessive moisture.

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168224440
B-18687692
Rev. 12/00
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