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# Eulexin* Tablets

BRAND OF FLUTAMIDE

FOR ORAL ADMINISTRATION

**DESCRIPTION:** Each EULEXIN Tablet contains 250 mg flutamide, an acetanilide, nonsteroidal, orally active antiandrogen. Other ingredients in EULEXIN Tablets include lactose, sodium lauryl sulfate, microcrystalline cellulose, starch, silicone dioxide and magnesium stearate.

**ACTIONS:** Flutamide demonstrates potent antiandrogenic effects by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues at the cellular level.

**INDICATIONS AND USAGE:** EULEXIN Tablets are indicated as monotherapy (with or without orchiectomy) or in combination with a luteinizing hormone-releasing hormone (LHRH) agonist for the management of advanced prostatic cancer in previously untreated patients or in those who have not responded or who have become refractory to hormonal manipulation.
As a component of the treatment used in the management of locally confined B2-C2 (T2b-T4) prostatic carcinoma, EULEXIN Tablets are also indicated to reduce tumor volume, to increase tumor control and to extend the disease-free interval.

**DOSAGE AND ADMINISTRATION:** The recommended dosage as monotherapy 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 EULEXIN Tablet therapy may be started 24 hours prior to initiation of the LHRH agonist.
In the management of locally confined prostatic carcinoma, the recommended dosage is one 250 mg tablet three times a day at eight-hour intervals. If an LHRH agonist is part of the treatment regimen, EULEXIN Tablets should be started simultaneously or 24 hours prior to initiation of the LHRH agonist. Administration of EULEXIN Tablets should begin eight weeks prior to radiation therapy and continue through the course of radiation therapy.

**DRUG INTERACTIONS:** Increases in prothrombin time have been noted in patients receiving warfarin therapy and flutamide therapy concomitantly. Therefore, close monitoring of prothrombin time is recommended and adjustment of the initiating or maintenance anticoagulant dose may be necessary.

**ADVERSE REACTIONS:**
Monotherapy: The most frequently reported adverse reactions to EULEXIN Tablets are gynecomastia and/or breast tenderness, sometimes accompanied by galactorrhea. These reactions disappear upon discontinuation of treatment or reduction in dosage.
EULEXIN Tablets demonstrate a low potential for cardiovascular liability, and when compared to diethylstilbestrol, this liability has been shown to be significantly lower.
Less frequent adverse reactions: diarrhea, nausea, vomiting, increased appetite, insomnia, tiredness, transient abnormal liver function and hepatitis. (See Additional Adverse Experiences and PRECAUTIONS sections for additional information on adverse reactions affecting the hepatic and biliary systems).
Rare adverse reactions: decreased libido, upset stomach, anorexia, ulcer-like pain, heartburn, constipation, edema, ecchymoses, herpes zoster, pruritus, lupus-like syndrome, headache, dizziness, weakness, malaise, blurred vision, thirst, chest pain, anxiety, depression, lymphedema.
Reduced sperm counts have been reported rarely.

Combination Therapy: The most frequently reported adverse effects experienced during combination therapy of EULEXIN Tablets with an LHRH agonist were hot flashes, decreased libido, impotence, diarrhea, nausea and vomiting. With the exception of diarrhea, these adverse experiences are known to occur with LHRH agonists alone, and at comparable frequency.
The high incidence of gynecomastia observed with flutamide monotherapy was reduced greatly in combination therapy. In clinical trials, no significant difference in gynecomastia incidence was observed between the placebo - and the flutamide -LHRH agonist treatment groups.
Rarely, patients experienced anemia, leukopenia, unspecified gastrointestinal disorders, anorexia, injection site irritation and rash, edema, neuromuscular symptoms, jaundice, genitourinary tract symptoms, hypertension, central nervous system adverse events (drowsiness, depression, confusion, anxiety, nervousness) and thrombocytopenia.

Additional Adverse Experiences: In addition, the following adverse experiences have been reported during world-wide marketing of EULEXIN 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.
Two reports of malignant male breast neoplasms in patients being dosed with EULEXIN Tablets have been reported. One involved aggravation of a preexisting nodule which was first detected three to four months before initiation of EULEXIN 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 EULEXIN 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.
Abnormal laboratory test values reported include changes in liver function, elevated blood urea nitrogen (BUN) and rarely, elevated serum creatinine.

**CONTRAINDICATIONS:** EULEXIN Tablets are contraindicated in patients exhibiting sensitivity reactions to flutamide or any component of this preparation.

**PRECAUTIONS:** Hepatic Injury: Treatment with EULEXIN should not be initiated in patients with serum transaminase levels exceeding 2 to 3 times the upper limit of normal. Periodic liver function tests must

be performed in all patients. Appropriate laboratory testing should be done monthly for the first 4 months, and periodically thereafter, and at the first symptom/sign of liver dysfunction (e.g., pruritus, dark urine, nausea, vomiting, 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, EULEXIN 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.

Flutamide did not demonstrate mutagenic potential in the Ames test, DNA repair test, in vivo sister chromatid exchange assay or the dominant lethal assay in rats.

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.

In combination therapy of EULEXIN Tablets administered with a LHRH agonist, the possible adverse effects of each product must be considered. The patient should not interrupt or alter the dosage regimen without consulting the physician.

EULEXIN is indicated only for use in male patients.

**PRECAUTIONS 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.

EULEXIN is indicated only for use in male patients.

**USE DURING PREGNANCY AND LACTATION:** No studies have been conducted in pregnant or lactating women. Therefore, the possibility that EULEXIN Tablets may cause fetal harm if administered to a pregnant woman, or may be present in the breast milk of lactating women, must be considered.

**OVERDOSAGE:** In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquilization, emesis and methemoglobinemia.

The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established.

Since flutamide is highly protein bound, dialysis may not be of any use as treatment for overdose. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care is indicated, including frequent monitoring of the vital signs and close observation of the patient.

**HOW SUPPLIED:** Packs of 20 and 100 tablets

**STORAGE:** Store between 2° and 30°C. Protect from light and excessive moisture.

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