

FUGEREL[®]

NAME OF MEDICINE

FUGEREL
Flutamide 250mg tablet

PRESENTATION

Tablets: Pale yellow, round, biconvex, 12.9mm diameter, scored on one side. Each tablet contains flutamide 250mg, lactose, sodium lauryl sulfate, microcrystalline cellulose, maize starch, colloidal anhydrous silica and magnesium stearate.

USES

ACTIONS

Flutamide demonstrates potent antiandrogenic effects by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues.

PHARMACOKINETICS

Analysis of plasma, urine and faeces of volunteers treated with tritium-labelled flutamide revealed that the drug is rapidly and completely metabolised. The major plasma metabolite, the alpha-hydroxylated derivative of flutamide, has comparable antiandrogenic activity. Both compounds disappear from plasma, with a half-life of 5 to 6 hours. One hour post-drug, flutamide accounted for 2.4% and hydroxyflutamide 22.9% of total plasma radioactivity.

Approximately 45% of the administered radioactive dose was excreted in urine and 2% in faeces during the first two post-drug days. Metabolism removed more than 50% of the radiolabelled resulting in an apparent slowing of excretion due to retention of the label as tritiated water. Correction for tritium exchange revealed that excretion is essentially complete within two days.

A distribution study in rats with ¹⁴C-flutamide showed that while flutamide concentration was generally low in all tissues examined, the metabolite hydroxyflutamide was present in concentrations up to 80 times the flutamide concentration by 6 hours after dosing. Hydroxyflutamide was relatively concentrated in the rat ventral prostate and seminal vesicles, demonstrated to be the target organs of pharmacological activity.

INDICATIONS

For the palliative treatment of advanced prostatic cancer in previously untreated patients or 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 advanced prostatic carcinoma.

DOSAGE AND ADMINISTRATION

The recommended dosage is one tablet three times a day at eight hourly intervals.

FUGEREL Tablets have been administered as monotherapy with or without surgical castration and in combination with medical (luteinising hormone-releasing hormone [LHRH] agonist) hormonal manipulation.

In combination with an LHRH agonist, treatment must be started simultaneously using both compounds, or FUGEREL Tablets may be started 24 hours prior to initiation of the LHRH agonist, to achieve the benefit of the adjunctive therapy.

In localised prostatic carcinoma, administration of FUGEREL and an LHRH agonist should begin eight weeks prior to radiation therapy and continue through the course of radiation therapy. Prior to radical prostatectomy, FUGEREL should be administered for 3 months.

CONTRAINDICATIONS

FUGEREL Tablets are contraindicated in patients exhibiting sensitivity reactions to flutamide or any components of this preparation.

WARNINGS AND PRECAUTIONS

Hepatic Injury:

Treatment with FUGEREL 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, 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, FUGEREL therapy should be discontinued if the patient develops jaundice or if the serum transaminase levels rise to 2 to 3 times the upper limit of normal, even in clinically asymptomatic patients. The hepatic conditions are usually reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with the use of flutamide.

In addition, in patients who have not received medical or surgical castration, periodic sperm count determinations may be considered during long-term treatment. In such patients, flutamide administration tends to elevate plasma testosterone and oestradiol levels.

When FUGEREL Tablets are administered in combination with LHRH agonists, the possible adverse effects of each product must be considered.

Precautions for Patients

Patients should be informed prior to initiating FUGEREL, 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 for concern), nausea, vomiting, persistent lack of appetite, yellow eyes or skin, tenderness in the right upper abdomen or "flu-like" symptoms.

Mutagenicity and Teratogenicity

Mutagenicity studies of flutamide have been conducted. Flutamide did not exhibit mutagenic potential in any of the test systems used.

Flutamide at doses of 25mg and 75mg/kg did not affect oestrous cycles or interfere with the mating behaviour of male and female rats.

Teratological effects were assessed in rats and rabbits. In pregnant rats, doses up to 200mg/kg did not result in the production of major malformations of offspring. At 100 and 200mg/kg, foetal growth was retarded and the antiandrogenic activity of the drug was evidenced by decreases in the anogenital distance. Survival rates were decreased. In rabbits, doses up to 15mg/kg did not affect the course of pregnancy or development of offspring. When administered to both male and female rats prior to and during the mating period, flutamide treatment at 25mg/kg reduced the pregnancy rate, but had no effect on the course of pregnancy, foetal development (except for the anticipated feminisation of males) or postnatal survival.

Carcinogenicity

Daily administration of flutamide to rats for 52 weeks at doses of 30, 90 or 180mg/kg/day, produced testicular interstitial adenomas at all doses.

In a 24-month carcinogenicity study conducted with male rats, daily administration of flutamide at doses of 10, 30 and 50mg/kg/day was associated with an increased number of testicular cell adenomas at all doses tested and with dose-related increases in mammary gland adenomas and carcinomas.

Two reports of malignant male mammary gland neoplasms have been reported in patients being treated with flutamide (see Adverse Reactions).

Use During Pregnancy and Lactation

FUGEREL is indicated only for use in male patients. No studies have been conducted in pregnant or lactating women. Therefore, the possibility that FUGEREL may cause foetal harm if administered to a pregnant woman, or may be present in the breast milk of lactating women, must be considered.

ADVERSE EFFECTS

Monotherapy

The most frequently reported adverse reactions to FUGEREL Tablets are gynaecomastia and/or breast tenderness, sometimes accompanied by galactorrhoea. These reactions usually disappear upon discontinuation of treatment or reduction in dosage.

Flutamide demonstrates a low potential for cardiovascular liability, and when compared to diethylstilbestrol this liability has been shown to be significantly lower.

Less frequent adverse reactions: diarrhoea, nausea, vomiting, increased appetite, insomnia, tiredness, transient abnormal liver function and hepatitis (*see Combination Therapy and Post-marketing Experience for additional information on liver and biliary system adverse reactions*).

Rare adverse reactions: decreased libido, upset stomach, anorexia, ulcer-like pain, heartburn, constipation, oedema, ecchymoses, herpes zoster, pruritus, lupus-like syndrome, headache, dizziness, weakness, malaise, blurred vision, thirst, chest pain, anxiety, depression, lymphoedema.

Reduced sperm counts have been reported rarely.

Combination Therapy

The most frequently reported adverse effects experienced during combination therapy of FUGEREL with an LHRH agonist were hot flushes, decreased libido, impotence, diarrhoea, nausea and vomiting. With the exception of diarrhoea, these adverse experiences are known to occur with LHRH agonists alone, and at comparable frequency.

The high incidence of gynaecomastia observed with FUGEREL monotherapy was markedly lower in combination therapy. In clinical trials, no significant difference in gynaecomastia incidence was observed between the placebo- and the flutamide-LHRH agonist treatment groups.

Very rarely, interstitial lung disease, hepatitis and photosensitivity have occurred.

Cardiovascular System

Common: Hypertension.

Central Nervous System

Common: Drowsiness, confusion, depression, anxiety, nervousness.

Gastrointestinal System

Common: Anorexia.

Hematopoietic System

Common: Anemia, leucopenia, thrombocytopenia.

Liver and Biliary System

Uncommon: Hepatitis, jaundice.

Other

Common: Oedema, genitourinary and neuromuscular symptoms.

Uncommon: Pulmonary symptoms.

Post-marketing Experience

In addition, the following spontaneous adverse experiences have been reported during world-wide marketing of FUGEREL: haemolytic anaemia, macrocytic anaemia, methaemoglobinaemia, sulphaemoglobinaemia, photosensitivity reactions (including erythema, ulcerations, bullous eruptions and epidermal necrolysis) and change in urine colour to an amber or yellow-green appearance which can be attributed to flutamide and/or its metabolites. Also observed were cholestatic jaundice, hepatic encephalopathy and hepatic necrosis. The hepatic conditions were usually reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with the use of flutamide.

Hyperglycemia and aggravation of diabetes mellitus have been reported very rarely.

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

Laboratory Tests

Abnormal laboratory test values reported include changes in liver function tests (e.g. elevated transaminases), elevated blood urea nitrogen (BUN) levels and rarely, elevated serum creatinine levels.

INTERACTIONS

It should be remembered that flutamide is an antiandrogen and as such may interact pharmacologically with androgens, oestrogens or other forms of hormonal therapy.

Clinical studies have suggested that flutamide, when used with LHRH agonists, may suppress any disease flare which may be caused by the LHRH agonist.

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

Cases of increased theophylline plasma concentrations have been reported in patients receiving concomitant theophylline and flutamide.

OVERDOSAGE

The single flutamide dose ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established. One patient survived after ingesting more than 5 grams of flutamide as a single dose. No adverse effects were observed.

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

Contact the Poisons Information Centre for advice regarding management of an overdose.

PHARMACEUTICAL PRECAUTIONS

Store below 30°C. Protect from excessive moisture. Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Bottle of 100 tablets (250mg)

FURTHER INFORMATION

Nil

NAME AND ADDRESS

Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149

DATE OF PREPARATION

17 October 2011

(ref. EXN CCDS Aug-2004 v2)