

Data Sheet

FLUTAMIN

Flutamide 250mg tablet

Presentation

Yellow, 12.5mm round, biconvex, standard concave tablets debossed with FT above the score and 250 below the score on one side of the tablet and G on the other side.

Uses

Actions

FLUTAMIN (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 intervals of eight hours.

Flutamide 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 flutamide 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 flutamide and an LHRH agonist should begin eight weeks prior to radiation therapy and continue through the course of radiation therapy. Prior to radical prostatectomy, flutamide should be administered for 3 months.

Contraindications

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

Warnings and Precautions

Hepatic Injury:

Treatment with flutamide 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, flutamide 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, periodic sperm count determinations in patients on long-term treatment with flutamide may be considered.

Since flutamide administration tends to elevate plasma testosterone and oestradiol levels, fluid retention may occur.

When flutamide 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 flutamide, 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 25 mg/kg and 75 mg/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 200 mg/kg did not result in the production of major malformations of offspring. At 100 mg/kg and 200 mg/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 15 mg/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 25 mg/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 180 mg/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 Effects).

Use during Pregnancy and Lactation:

Flutamide is indicated only for use in male patients. No studies have been conducted in pregnant or lactating women. Therefore, the possibility that flutamide 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

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

Less frequent adverse reactions: diarrhoea, nausea, vomiting, increased appetite, insomnia, tiredness, transient abnormal liver function and hepatitis.

Rare adverse reactions: 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, decreased libido, lymphoedema.

Reduced sperm counts have been reported rarely in long-term treatment.

Usually these reactions have not been of sufficient severity to require dosage reduction or discontinuation of treatment. If adverse reactions are severe, a reduction in dosage, without loss of efficacy, may be beneficial.

In addition, haemolytic anaemia, macrocytic anaemia, methaemoglobinaemia, sulfhaemoglobinaemia, 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.

Flutamide tablets demonstrate a low potential for cardiovascular liability, and when compared to diethylstilboestrol, this liability has been shown to be significantly lower. Although there have been reports of cardiovascular adverse events in patients on flutamide therapy, the relation of these to flutamide has not yet been elucidated.

Hyperglycaemia, interstitial lung disease 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 gynaecomastia 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 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 overdosage or considered to be life-threatening has not been established. One patient survived after ingesting more than 5g of flutamide as a single dose. No adverse effects were observed.

Treatment:

As in the management of overdosage 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.

Pharmaceutical Precautions

Store below 30 °C. Protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

Blister strip packs: 100's

Further Information

Nil.

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