

NEW ZEALAND DATA SHEET

FLUTAMIN

Flutamide 250mg tablet



Presentation

Yellow, 12.5mm round, biconvex 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.

Pharmacology

Flutamide exhibits specific antiandrogenic effects, largely directed to the prostate as target organ. Flutamide, administered orally to intact immature male rats at doses ranging from 1 to 25mg/kg, significantly reduced prostate and seminal vesicle weights. Other endocrine structures were not altered. In studies of dogs with benign prostatic hypertrophy, daily oral administration of flutamide (5 to 50mg/kg) for six weeks reduced the size of the prostate gland and reversed the associated histologic and histochemical changes.

Studies of the mechanism of flutamide's antiandrogenic action on the ventral prostate gland of the rat indicate that it either inhibits androgen uptake or blocks nuclear binding of androgens in target tissues. While flutamide exerts antiandrogenic action on the accessory sex structures, it did not decrease sexual activity or spermatogenesis in male rats at pharmacologically active doses.

Flutamide exhibits specific activity towards androgen-dependent receptors with little effect on other hormonal receptors. It lacks estrogenic, antiestrogenic, progestational and antiproggestational activities.

Pharmacokinetics

Analysis of plasma, urine and feces of three male volunteers following a single oral 200mg dose of tritium-labelled flutamide revealed that the drug is rapidly and completely absorbed and excreted mainly in the urine. At least six metabolites have been identified in plasma. The distribution and elimination half-lives for flutamide are 0.8 and 7.8 hours respectively, and the corresponding half-lives for its active metabolite, 2-hydroxyflutamide, are 1.7 and 8.1 hours respectively. The major urinary metabolite is 2-amino-5-nitro-4-(trifluoromethyl)phenol.

Tissue distribution of flutamide was examined in male rats given an oral dose of ¹⁴C-flutamide at 5mg/kg. 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, hydroxyflutamide, was present at higher concentrations than flutamide in all tissues studied.

Hydroxyflutamide was relatively concentrated in the rat ventral prostate gland and seminal vesicles, previously demonstrated to be the target organs of pharmacological activity. It was similarly concentrated in the rat pituitary gland.

The very rapid and almost complete conversion of flutamide to metabolites strongly suggests that the biological activity shown by this substance is due to an active metabolite. Hydroxyflutamide is the major metabolite in man and laboratory animals, and has been shown to possess potent antiandrogenic 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, flutamide tablets should 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.

Flutamide is also contraindicated in patients with severe hepatic impairment.

Warnings and Precautions

Flutamide is indicated only for use in male patients.

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

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

Hepatic Injury

There have been post-marketing reports of hospitalisation 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 usually reversible after prompt discontinuation of therapy. Approximately half of the reported cases of hepatic injury occurred within the initial 3 months of treatment with flutamide.

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. Liver function tests should be followed-up closely until resolution.

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 – see Adverse Effects), nausea, vomiting, persistent lack of appetite, yellow eyes or skin, tenderness in the right upper abdomen or “flu-like” symptoms.

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 in 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

Cholestatic jaundice, hepatic encephalopathy and hepatic necrosis have been reported. 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.

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

The most frequently reported adverse reactions to flutamide monotherapy are gynecomastia and/or breast tenderness, sometimes accompanied by galactorrhea. These are greatly reduced when flutamide tablets are administered concomitantly with an LHRH agonist.

Central nervous system reactions including drowsiness, confusion, depression, anxiety and nervousness have also been reported.

Two cases of pulmonary embolism have been reported in patients receiving flutamide but a relationship to flutamide has not been established. Very rarely, interstitial lung disease has occurred.

Other Adverse Reactions

Other less frequent adverse reactions reported with flutamide monotherapy and/or combination therapy include:

Gastrointestinal:

Constipation, increased appetite, anorexia

Central Nervous System:

Insomnia, tiredness, headache, dizziness, malaise, depression

Skin and subcutaneous tissue disorders:

Ecchymoses, herpes zoster, pruritus

Haematological:

Anemia, leucopenia, thrombocytopenia, haemolytic anemia, macrocytic anemia, methaemoglobinemia, sulfhaemoglobinemia Others:

Peripheral oedema, photosensitivity reactions (including erythema, ulcerations, bullous eruptions and epidermal necrolysis), injection site irritation and rash associated with the administration of the LHRH agonist. Change in urine colour to an amber or yellow-green appearance which can be attributed to flutamide and/or its metabolites. Usually these other 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.

Hyperglycaemia and aggravated diabetes mellitus have been reported very rarely.

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

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 one month of treatment, the nodule was excised and was diagnosed as a poorly differentiated ductal carcinoma. The other report involved a patient who developed gynaecomastia and a breast 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. Changes in liver function tests have been observed in 3 to 31% of patients treated with flutamide monotherapy.

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.

Flutamide inhibits steroid metabolism in rat testicular microsomes and alters their content of cytochrome P-450. Although this may be organ specific, an effect on liver microsomes has not been excluded, so the metabolism of some drugs by the liver may be affected by flutamide. Although data are not available on potential interaction between flutamide and paracetamol, opioid analgesics or non-steroidal anti-inflammatory agents, flutamide may affect the metabolism of these drugs which are frequently administered to patients with prostate cancer.

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 5 grams 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. Since flutamide is highly protein bound, dialysis may not be of any use as treatment for an overdose.

Pharmaceutical Precautions

List of excipients

Lactose monohydrate, maize starch, pre-gelatinised maize starch, cellulose, sodium lauryl sulfate, silica, magnesium stearate

Special precautions for storage

Store below 30 °C. Protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

Blister packs of 100 tablets

Further Information

Nil.

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