AUSTRALIAN PRODUCT INFORMATION

FLUTAMIN

(flutamide) tablet

1 NAME OF THE MEDICINE

Flutamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of flutamide as the active ingredient.

Excipients with known effect: sulfites and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

FLUTAMIN 250 mg: 12.5mm, biconvex, round, yellow tablet, debossed "FT" breakline “250” on one side, “G” on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For use in combination with an LHRH agonist for the management of advanced prostatic carcinoma in previously untreated patients.

Prevent disease flare associated with the use of LHRH agonists.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage is one tablet three times a day at 8 hourly intervals. FLUTAMIN should be started up to 24 hours prior to the initiation of the LHRH agonist.

4.3 CONTRAINDICATIONS

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

FLUTAMIN is also contraindicated in patients with severe hepatic impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular

Based on studies conducted in the literature, combined androgen blockade with an anti-androgen plus LHRH analogue may increase risk of cardiovascular disease (heart attack, cardiac failure, sudden cardiac death) and adversely affects independent cardiovascular risk factors (serum lipoproteins, insulin sensitivity and obesity). Physicians should carefully consider whether the benefits of combined androgen blockade outweigh the potential cardiovascular risk. Assessment of cardiovascular risk factors, monitoring for signs and symptoms suggestive of development of cardiovascular disease, and management according to local clinical practice and guidelines should be considered.

Effect on QT/QTc interval

The potential for QT/QTc prolongation has not been studied with flutamide tablets. Combined androgen blockade studies with other anti-androgen plus LHRH analogue or surgical castration have been associated with the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome,

electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications.

Endocrine and Metabolism

A reduction in glucose tolerance and/or glycated hemoglobin (HbAlc) has been observed in males receiving combined androgen blockade. This may manifest as diabetes or loss of glycemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose and/or glycated hemoglobin (HbAlc) in patients receiving flutamide tablets in combination with LHRH analogues.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Musculoskeletal/Changes in Bone Density

Based on studies conducted in the literature, decreased bone mineral density can be anticipated with long term combined androgen blockade with an anti-androgen plus LHRH analogue. Combined androgen blockade is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal fracture increases with the duration of combined androgen blockade. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, combined androgen blockade may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy is instituted.

When FLUTAMIN is administered in combination with an LHRH agonist, the possible adverse effects of each product must be considered.

FLUTAMIN is indicated only for use in male patients

Use in Hepatic Impairment

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 necrosis, 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 three 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 sign/symptom 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, FLUTAMIN therapy should be discontinued immediately 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.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

Abnormal laboratory test values reported include changes in liver function tests (in 3 to 31% of patients treated with flutamide monotherapy), elevated blood urea nitrogen (BUN) levels, and rarely elevated serum creatinine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

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.

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

The potential for QT/QTc prolongation has not been studied with flutamide tablets. Since combined androgen blockade prolongs the QTc interval, the concomitant use of flutamide tablets or capsules with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: No data available

No studies have been conducted in pregnant or lactating women. Therefore, the possibility that FLUTAMIN may cause foetal harm if administered to a pregnant woman or may be present in the breast milk of lactating women, must be considered.

Use in Lactation

See above.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

The most frequently reported adverse effect experienced during combination therapy of flutamide with LHRH agonists 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 most frequently reported adverse reactions to flutamide monotherapy are gynaecomastia and/or breast tenderness, sometimes accompanied by galactorrhoea; these are greatly reduced when flutamide tablets are administered concomitantly with an LHRH agonist.

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.

Hypertension has also been reported as a common adverse effect.

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

Nervous System disorders:

insomnia; tiredness; headache; dizziness; malaise, drowsiness, confusion, depression, anxiety, nervousness.

Cardiac disorders:

QT interval prolongation.

Gastrointestinal disorders:

anorexia; constipation.

Haematological:

anaemia; leucopenia; thrombocytopenia; haemolytic anaemia; macrocytic anaemia; methaemoglobinaemia, sulfhaemoglobinaemia.

Other:

peripheral oedema; genitourinary; neuromuscular symptoms; photosensitivity reactions (including erythema, ulcerations, bullous eruptions and epidermal necrolysis); change in urine colour to an amber or yellow-green appearance which can be attributed to flutamide and/or its metabolites; injection site irritation and rash associated with the administration of the LHRH agonist. 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. Hyperglycemia and aggravated diabetes have been reported very rarely.

Two cases of malignant breast neoplasms in patients being treated with flutamide have been reported. One involved 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 case was a patient who developed gynaecomastia and a breast nodule after two and six months treatment respectively with flutamide monotherapy for 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

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, 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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

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 25 mg/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 50 mg/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 antiprogestational activities.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Analysis of plasma, urine and faeces of three male volunteers following a single oral 200 mg 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 5 mg/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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

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 50 mg/kg/day was associated with an increased number of testicular interstitial 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain lactose monohydrate, microcrystalline cellulose, maize starch, pregelatinised maize starch, sodium lauryl sulfate, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Aluminium/PVC blister pack

Pack sizes: 100

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

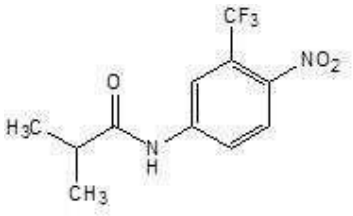
AUST R 65675 – FLUTAMIN flutamide 250mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical Name

2-methyl-N-[4-nitro-3-(trifluoromethyl)-phenyl]propanamide

CAS Number

13311-84-7

Molecular formula

$C_{11}H_{11}F_3N_2O_3$

Molecular weight

276.22

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

24/03/1999

10 DATE OF REVISION

17/06/2024

Summary Table of Changes

Section Changed	Summary of New Information
6.4	Update storage condition

FLUTAMIN is a Viatris company trade mark

FLUTAMIN_pi\Jun24/00 (CCDS 30-May-2023)