NEW ZEALAND DATA SHEET

FLUTAMIN

1. Product Name

Flutamin, 250 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 250 mg of flutamide.

Excipients with known effect: sulfites and sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Yellow, 12.5 mm 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.

4. Clinical Particulars

4.1 Therapeutic 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.

4.2 Dose and method of 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.

4.3 Contraindications

Flutamide tablets are contraindicated in patients exhibiting sensitivity reactions to flutamide or any components of this preparation in section 6.1.

Flutamide is also contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

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.

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 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 section 4.8), nausea, vomiting, persistent lack of appetite, yellow eyes or skin, tenderness in the right upper abdomen or “flu-like” symptoms.

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.

Use in the elderly

No data available.

Paediatric use

No data available

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.

4.5 Interaction with other medicines and other forms of interaction

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.

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.

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.

Use in lactation

See above.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, confusion, tiredness, or blurred vision and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 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.

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, drowsiness, confusion, depression, anxiety, nervousness

Skin and subcutaneous tissue disorders:
Ecchymoses, herpes zoster, pruritus

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

Others:
Peripheral oedema, genitourinary, neuromuscular symptoms, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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.

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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-androgens, ATC code: L02BB01

Mechanism of action

FLUTAMIN (flutamide) demonstrates potent antiandrogenic effects by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues.

Pharmacodynamic effects

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 feces 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 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).

6. Pharmaceutical Particulars

6.1 List of excipients

Flutamin tablet also contains:

- lactose monohydrate
- maize starch
- pre-gelatinised maize starch
- micro crystalline cellulose
- sodium lauryl sulfate
- silica-colloidal anhydrous
- magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30°C. Protect from light.

6.5 Nature and contents of container

Al/PVC blister pack of 100 tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

11 March 1999

10. Date of Revision of the Text

13 June 2022

Sections	
2	Declaration of allergens.
6.1	Removed gluten free statement.
8	Updated sponsor detail.