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: maize starch and lactose.

Allergen Declaration: Contains sulfites and sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

A yellow 0.4921" (12.5 mm) round, biconvex, tablet 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.

When flutamide is used in combination with an LHRH agonist from the outset, the flare reaction can be reduced if flutamide is initiated before the LHRH agonist. Therefore, it is recommended to start flutamide either at the same time or at least 24 hours before the LHRH agonist.

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.

Special populations

Hepatic impairment

In patients with impaired liver function, long-term treatment with flutamide should only be initiated after careful assessment of the individual benefits and risks.

Renal impairment

Flutamide should be administered with caution in patients with impaired renal function.

Method of administration

For oral use only.

The tablet should ideally be taken after meals.

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, cholestatic 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 or the dose reduced. 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. Theophylline is metabolised mainly by CYP1A2, the main enzyme responsible for converting flutamide to its active metabolite 2-hydroxyflutamide.

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

Fertility

No data available.

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.

Breastfeeding

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

Adverse reactions are listed below by MedDRA system organ class. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred term
Blood and lymphatic system disorders	Common	Anaemia, leukopenia, thrombocytopenia
Metabolism and nutrition disorders	Very rare	Hyperglycemia, worsening of diabetes mellitus
Nervous system disorders	Common	Confusional state, depression, anxiety, nervousness, somnolence
Cardiac disorders	Not known	QT interval prolongation
Vascular disorders	Very common	Hot flushes
	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary symptoms
Gastrointestinal disorders	Very common	Diarrhoea, nausea/vomiting,
	Uncommon	Decreased appetite.
Hepatobiliary disorders	Uncommon	Hepatitis and jaundice
Skin and subcutaneous tissue disorders	Very rare	Photosensitivity

System Organ Class	Frequency	Preferred term
Musculoskeletal and connective tissue disorders	Common	Neuromuscular symptoms
Renal and urinary disorders	Common	Genitourinary symptoms
Reproductive system and breast disorders	Very common	Decreased libido, erectile dysfunction
	Common	Gynecomastia
General disorders and administration site conditions	Common	Fatigue, oedema
	Uncommon	Malaise

Cases of haemolytic anaemia, macrocytic anaemia, methaemoglobinaemia, photosensitivity and discolouration of the urine have also been reported.

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

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

Haematological:
Sulfhaemoglobinemia

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.

Cases of cholestatic jaundice, encephalopathy and hepatic necrosis have also been reported. Although these liver abnormalities were usually reversible upon discontinuation of flutamide, there have been reports of death from acute hepatic failure associated with the use of this medicinal product.

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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Clinical trials have been conducted with flutamide at doses up to 1,500 mg per day for periods of up to 36 weeks with no reports of serious adverse reactions. The adverse reactions reported were gynaecomastia, breast sensitivity and some increases in AST. The acute toxicity dose of flutamide in humans has not been established. One patient survived after ingesting more than 5 grams of flutamide as a single dose with no apparent adverse effects.

Treatment

As in the management of an overdosage with any medicine, 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 and cytoplasmic 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

In clinical trails performed with flutamide combined with LHRH agonists as neoadjuvant therapy for locally confined prostate cancer, pre-radical surgery or radiotherapy, an increase in the survival rate

was note demonstrated, although a decrease in tumour size, a reduction in morbidity and surgical consequences and a delay in disease progression were witnessed.

5.2 Pharmacokinetic properties

Absorption

After oral administration, flutamide is rapidly and completely absorbed and almost completely metabolised.

Distribution

Flutamide is highly protein bound (94-96%) and its active metabolite is 92-94% protein bound. The maximum plasma concentration of hydroxyflutamide at steady state at the recommended therapeutic dose (250 mg three times daily) is approximately 1.7 mg/L.

Biotransformation

The major metabolite is hydroxyflutamide, which has been shown to have potent antiandrogenic activity. Studies with radiolabelled flutamide revealed rapid and extensive conversion to its metabolites, with at least six identified in plasma up to 8 hours after administration.

Elimination

Approximately 45% of the administered dose is excreted in the urine and 2% in the faeces during the first two days. Excretion and metabolism are essentially completed within two days. The plasma elimination half-life is 5 to 6 hours in adults for flutamide and its major metabolite, hydroxyflutamide, and 8 hours in the elderly. The elimination half-life at steady state is approximately 10 hours.

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 25°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
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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

7 November 2023

Summary table of changes

Sections	Summary of new information
4.2	Updated information on Flutamide use in combination with LHRH agonist. Addition of use in hepatic impairment, and renal impairment patients Addition of Method of Administration

4.4, 4.9	Minor editorial update
4.4	Updated information regarding use in hepatic impairment
4.5	Addition of use in conjunction with theophylline
4.8	ADRs presented in MedDRA format, aligning with CCDS. Addition of ADRs related to liver abnormalities. Updated ADR reporting website
4.9	Additional information regarding overdosage observed in clinical trials.
5.1	Addition of Clinical trials information
5.2	Addition of subheadings, aligning with CCDS.