SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flutamide 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250.00 mg of flutamide (INN)

Excipient with known effect:
Each tablet contains 222 mg lactose monohydrate

For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Flutamide 250 mg Tablets is an uncoated immediate-release tablet for oral use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced prostate cancer in which suppression of testosterone effects is indicated: as initial treatment in combination with an LHRH-agonist; as adjunctive therapy in patients already receiving LHRH-agonist therapy; in surgically castrated patients; in the treatment of patients who have not responded to other forms of hormonal manipulation or in patients who cannot tolerate such treatment.

4.2 Posology and method of administration

Posology

One tablet three times daily. When used as initial treatment with an LHRH-agonist, a greater reduction in the incidence and severity of the LHRH-agonist flare reaction may be achieved if Flutamide 250 mg Tablets is introduced before rather than concomitantly with the agonist.

It is, therefore, recommended that Flutamide 250 mg Tablets, one tablet three times daily should be started at least three days before an LHRH-agonist and continued thereafter at the same dose.

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

Flutamide 250 mg Tablets should be administered with caution in patients with impaired renal function.

Method of Administration

The tablets are to be taken preferably after meals.

4.3 Contraindications

Flutamide is contraindicated in patients who are hypersensitive to flutamide or any other component of this preparation. If hypersensitivity reactions occur, Flutamide must be withdrawn immediately.

4.4 Special warnings and precautions for use

Hepatic injury: In cases where impaired hepatic function exists, chronic flutamide therapy should only be used after a careful evaluation of the benefit-risk ratio. Liver function tests should be performed before treatment is started. Treatment with flutamide should not be started if the patient`s serum transaminase values are more than two- to threefold normal values.

Since transaminase abnormalities, cholestatic jaundice, hepatic encephalopathy, and liver cell necrosis have been observed with the use of flutamide, periodic liver function tests should be considered. Hepatotoxicity, which may be fatal, may occur after several weeks or months of therapy. The hepatic conditions were usually reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with use of flutamide.

Appropriate laboratory liver function tests should be done for every patient once monthly for the first 4 months and then periodically or when first

sign/symptoms of liver dysfunction (e.g. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms) occur. Flutamide therapy should be discontinued if the patient has laboratory evidence of liver injury or clinical jaundice in the absence of biopsy-confirmed liver metastases, or if the serum transaminase values exceed two-to threefold normal values in patients without pathological findings.

Patients should be advised to discontinue flutamide therapy and seek medical advice immediately if any symptoms or signs suggestive of hepatotoxicity occur.

In patients who have not received medical or surgical castration, periodic sperm-count determination may be considered during long-term treatment. In such patients flutamide administration tends to elevate plasma testosterone and oestradiol levels, fluid retention may occur, thus the drug should be used with caution in cardiovascular disease.

Flutamide may lead to elevated testosterone and estradiol plasma levels, resulting in fluid retention. In severe cases this can lead to an increased risk of angina and heart failure. Therefore, flutamide should be used with caution in the presence of cardiovascular disease. Flutamide can exacerbate oedema or ankle swelling in patients prone to these conditions.

An increase in estradiol levels may predispose to thromboembolic events.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Flutamide.

Androgen depletion therapy is known to reduce bone mineral density and increase the risk of osteoporotic fractures. In recent studies this has been seen in patients treated with LHRH analogues plus flutamide. These complications may be potentiated when patients are already osteoporotic due to their advanced age at diagnosis of prostate cancer.
Bone mineral density (BMD) should be measured regularly to identify patients at higher risk for fractures. BMD should be measured at baseline, and then a year later as a minimum. Further measurements can be considered at yearly intervals in men with BMD approaching osteoporosis or those with decreased bone mineral density in whom life expectancy warrants it.

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

Flutamide is indicated only for use in male patients.

Contraceptive measures should be taken during treatment.

There have been cases of interstitial pneumonitis reported in patients undergoing treatment with flutamide. Patients should be monitored for the development of respiratory symptoms such as dyspnoea during the first few weeks of therapy.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between flutamide and leuprolide have not occurred, however, in combination therapy of flutamide administered with an LHRH agonist, the possible adverse effects of each product must be considered.

Increases in prothrombin time have been reported in patients receiving oral anticoagulant therapy after flutamide monotherapy was initiated. Therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Flutamide 250 mg Tablets is administered concomitantly with oral anticoagulants.

Cases of increased theophylline plasma concentrations have been reported in patients receiving concomitant theophylline and Flutamide treatment. Theophylline is primarily metabolised by CYP 1A2 which is the primary enzyme responsible for the conversion of Flutamide to its active agent 2-hydroflutamide.

Concurrent administration of other potentially hepatotoxic drugs should be undertaken only after careful assessment of benefits and risks.

Given the known potential liver and renal toxicities of the product, excessive consumption of alcohol should be avoided.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Flutamide with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Flutamide 250 mg Tablets is only indicated for use in male patients. Contraceptive measures should be taken during treatment.

Flutamide tablets may cause foetal harm when administered to a pregnant woman. In animal studies, the reproductive toxicity of flutamide was associated with the antiandrogenic activity of this agent. There was decreased 24-hour survival in the offspring of rats treated with flutamide at doses of 30, 100, or 200 mg/kg/day (approximately 3, 9, and 19 times the human dose) during pregnancy. A slight increase in minor variations in the development of the sternebra and vertebra was seen in foetuses of rats at the two higher doses. Feminisation of the males also occurred at the two higher dose levels. There was a decreased survival rate in the offspring of rabbits receiving the highest dose (15 mg/kg/day; equal to 1.4 times the human dose).

The safety of Flutamide 250 mg Tablets for use in human pregnancy or lactation has not been established. Therefore, the possibility that flutamide tablets may cause foetal harm if administered to a pregnant women, or may be present in the breast milk of lactating women, must be considered.

4.7 Effects on ability to drive and use machines

No studies on effects on the ability to drive and use machines have been performed with flutamide. However, possible adverse reactions such as fatigue, dizziness and confusion have been reported and may impair the ability to drive and use machines.

4.8 Undesirable effects

Frequency classification:
Very common - >1 in 10
Common - >1 in 100 but <1 in 10
Uncommon - >1 in 1000 but <1 in 100
Rare – >1 in 10,000 but <1 in 1000
Very Rare - <1 in 10,000
Not known – (cannot be estimated from the available data)

Monotherapy

SOC	**Frequency**	**Reactions**
Infections and infestations	Rare	Herpes zoster
Neoplasms benign and malignant	Very rare	Malignant male breast neoplasms*
Blood and lymphatic system disorder	Rare	Oedema, ecchymoses, lymphoedema
Immune system disorders	Rare	Lupus-like syndrome

Metabolism and nutrition disorders	Common	Increased appetite
	Rare	Anorexia
Psychiatric and Nervous system disorders	Common	Insomnia.
	Rare	Anxiety, depression, dizziness
Eye disorder	Rare	Blurred vision
Respiratory, Thoracic and Mediastinal disorders	Rare	Interstitial pneumonitis, dyspnoea
	Very rare	Cough
Cardiac and vascular disorders	Rare	Cardiovascular disorders, hypertension.
	Not known	QT prolongation (see sections 4.4 and 4.5)
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea,
	Rare	Constipation, ulcer-like pain, thirst, dyspepsia, colitis, upset stomach, heartburn
Hepato-biliary disorders	Rare	Hepatitis, liver function test abnormalities. See 4.4 Special warnings and precautions for use.
Skin and subcutaneous tissue disorders	Rare	Urticaria, pruritus, alteration of the hair growth pattern and loss of hair (head).
	Very rare	Photosensitivity
Musculoskeletal, Connective tissue and bone disorders	Rare	Muscle cramps
Renal and Urinary disorders	Very Rare	Acute renal failure
Reproductive system and breast disorders	Very common	Gynaecomastia, breast tenderness, galactorrhoea. (These reactions disappear upon discontinuation of treatment or dosage reduction).
	Rare	Reversible increase of serum testosterone levels. Reduced sperm counts, decreased libido.
General Disorders	Common	Somnolence, tiredness
	Rare	Asthenia, headache, dizziness, chest pain, malaise, hot flushes, weakness.
Investigations	Common	Transient abnormal liver function

Combination Therapy

SOC	**Frequency**	**Reactions**
Blood and lymphatic system disorders	Rare	Anaemia, leukopenia, thrombocytopenia, oedema.
	Very rare	Haemolytic anaemia, macrocytic anaemia, methemoglobinaemia, sulfhemoglbinaemia
Metabolism and nutrition disorders	Rare	Anorexia

	Very rare	Hyperglycemia, aggravation of diabetes mellitus
Reproductive system and breast disorders	Very common	Hot flushes, decreased libido, impotence.
	Rare	Gynaecomastia
Psychiatric and Nervous system disorders	Rare	Drowsiness, depression, confusion, anxiety, nervousness.
Cardiac and Vascular disorders	Very Rare	Pulmonary symptoms, such as dyspnoea and hypertension.
Respiratory, thoracic and mediastinal disorders	Very Rare	Interstitial lung disease
Gastrointestinal disorders	Very Common	Nausea, vomiting, diarrhoea
	Rare	Unspecified gastrointestinal disorders, abdominal pain.
Hepato-biliary disorders	Rare	Hepatitis, jaundice
	Very rare	Cholestatic jaundice, hepatic encephalopathy, hepatic necrosis, cases of severe hepatic injury with some fatal outcomes.
Skin and Subcutaneous tissue disorders	Rare	Rash
	Very rare	Photosensitivity, erythema, ulcerations, bullous eruptions, epidermal necrolysis
Musculoskeletal, Connective tissue and Bone disorders	Rare	Neuromuscular symptoms, Reduced bone mineral density, osteoporotic disorders, arthralgia, myalgia.
Renal and Urinary disorders	Rare	Genitourinary tract symptoms, dysuria, changes in urinary frequency, change in urine colour to amber or yellow-green.
	Very Rare	Acute renal failure
General disorders	Rare	Injection site irritation
Investigations	Common	Changes in liver function
	Very rare	Elevated blood urea nitrogen (BUN), elevated serum creatinine

*Few reports of malignant male breast neoplasms in patients being dosed with flutamide tablets 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 bening prostatic hypertrophy. After excision, this was diagnosed as a poorly differential ductal carcinoma. The other report involved gynaecomastia and a nodule noted two and six months, respectively, after initiation of flutamide monotherapy for the 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.

The high incidence of gynaecomastia seen with flutamide monotherapy is generally reduced with combination therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquilization, emesis and methemoglobinaemia.

Clinical trials have been conducted with flutamide tablets in doses up to 1500 mg per day for periods up to 36 weeks with no serious adverse effects reported. Those adverse reactions reported included gynaecomastia, breast tenderness and some increases in SGOT.

The single dose of flutamide tablets ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established. One patient survived after the ingestion of a single dose of 5 g flutamide - no side effects could be observed.

Management

Since flutamide is highly protein bound, dialysis may not be of any use for overdose treatment. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Gastric lavage may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anti-Androgens, ATC - Code L02 B B01

Flutamide is a non-steroidal antiandrogenic substance.

In animal studies, flutamide demonstrates potent antiandrogenic effects. It has been demonstrated to reduce prostate and seminal vesicle weights in intact immature rats and to prevent androgen-stimulated hypertrophy of these organs in castrated immature rats. Prostate weights in dogs and baboons were also reduced by flutamide treatment. It exerts its antiandrogenic effects attributable to its pharmacologically active metabolite, hydroxyflutamide, by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgens in target tissues. When flutamide is given in combination with surgical or medical castration, suppression of both testicular and adrenal androgen activity is achieved. Because flutamide is non-steroidal, Flutamide 250 mg Tablets demonstrates a low potential for cardiovascular side-effects.

5.2 Pharmacokinetic properties

Flutamide is rapidly metabolised to the biologically active a-hydroxylated derivative, 2-hydroxyflutamide. In a study with tritium labelled flutamide (210 mg po), peak plasma concentrations for flutamide and its main metabolite were 48 and 558 ng/ml, respectively and occurred 1 hour after the dose. Ninety-one % of the dose was eliminated in two days, mainly via the urine.

Flutamide and 2-hydroxyflutamide are >90 % bound to plasma proteins at steady state concentrations.

Flutamide administered at a dose of 3 x 250 mg every 8 hours for 5 to 6 days revealed a steady state concentration of the active metabolite 2-hydroxyflutamide of 940 ng/ml after 2 to 4 days, whereas flutamide in its intact form could not be detected at the end of each 8-hour interval.

The elimination half-life for 2-hydroxyflutamide was 4.3 - 6.6 hours after a single 250 mg dose and 8.4-21.9 hours after a single 500mg dose.

Absorption and excretion of the drug were not significantly different in patients undergoing combination therapy with flutamide (750 mg/day, 6 patients) and an LHRH agonist or in healthy volunteers who were treated exclusively with flutamide (single dose 250 mg, 6 patients).

5.3 Preclinical safety data

Carcinogenesis. Mutagenesis. Impairment of Fertility:

Daily administration of flutamide to rats for 52 weeks at doses of 30, 90 or 180 mg/kg/day

(approximately 3, 8 or 17 times the human dose), produced testicular interstitial cell

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 (i.e. up to approximately 5 times the human dose) 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/or carcinomas.

Flutamide did not demonstrate mutagenic activity in the Ames Salmonella/ typhimurium mutagenesis assay. Dominant lethal tests in rats were negative.

Reduced sperm counts were observed during a 6-week study of flutamide monotherapy in normal human volunteers. Flutamide did not affect oestrus cycles or interfere with the mating behaviour of male and female rats when the drug was administration at 25 and 75 mg/kg/day prior to mating. Males treated with 150 mg/kg/day (30 times the minimum effective antiandrogenic dose) failed to mate; mating behaviour returned to normal after dosing was stopped. Conception rates were decreased in all dosing groups. Suppression of spermatogenesis was observed in rats dosed for 52 weeks at approximately 3,8 or 17 times the human dose and in dogs dosed for 78 weeks at 1.4, 2.3 and 3.7 times the human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, sodium lauryl sulphate, microcrystalline cellulose, maize starch, colloidal anhydrous silica, magnesium stearate.

6.2 Incompatibilities

None

6.3 Shelf life

The proposed shelf-life of the product as packaged for sale is 36 months.

6.4 Special precautions for storage

Flutamide 250 mg Tablets should not be stored above 25ºC. Store in a dry place in its original package, the outer carton ensuring sufficient protection from light.

6.5 Nature and contents of container

The container is a blister strip consisting of coloured PVC and aluminium and contains 21 tablets. Boxes containing 4 strips (84 tablets) are available.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Waymade Plc
Trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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