SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flutamide 250mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg flutamide

Excipient with known effect: Each tablet contains 221.7 mg of lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Yellowish, round biconvex tablets with score notch on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flutamide is indicated for the treatment of advanced prostatic carcinoma in which suppression of testosterone effects is indicated. Flutamide may be used in combination with an LHRH agonist, both on commencement of treatment or as an adjunctive therapy in patients already receiving an LHRH agonist. Flutamide may also be used in surgically castrated patients.

4.2 Posology and method of administration

Posology

Adults and older people:

One 250mg tablet 3 times daily at 8 hour intervals

When Flutamide is used as initial treatment with an LHRH agonist, a reduction in severity of the flare reaction may be achieved if treatment with Flutamide is initiated before the LHRH agonist. Consequently, it is recommended that treatment with Flutamide should commence simultaneously or at least 24 or more hours before the LHRH agonist.
The administration of Flutamide should begin eight weeks prior to radio therapy and continue for its duration, or for 12 weeks pre-prostatectomy.

Method of administration

For Oral use.

The tablets are to be taken preferably after food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic injury:
Flutamide may be hepatotoxic and should be used with caution in patients with pre-existing hepatic dysfunction only after considering the benefits and potential risks.

There have been reports of elevated serum transaminase levels, cholestatic jaundice, hepatic necrosis and hepatic encephalopathy associated with Flutamide treatment. The hepatic effects were usually reversible following discontinuation of flutamide, although cases have been reported of death after severe liver damage linked to the use of flutamide. Hepatotoxicity, which may be fatal, may occur after several weeks or months of therapy. Hepatic function should be monitored regularly before, during and after initiation of Flutamide therapy. Treatment with Flutamide should not be initiated in patients with serum transaminase levels exceeding 2-3 times the upper limit of normal.

Periodic liver function tests must be performed before initiation and during treatment, especially in patients receiving long term treatment with flutamide. Appropriate laboratory liver function tests should also be performed for every patient once a month for the first 4 months and then periodically or when the first sign or symptom of hepatic dysfunction occur (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms).

Patients should be advised to discontinue Flutamide therapy and seek medical advice immediately if any symptoms or sign suggestive of hepatotoxicity occur. If the patient presents liver function test results indicative of liver damage, clinical jaundice in the absence of hepatic metastasis confirmed by biopsy, or serum transaminase levels of 2 to 3 times above the normal limits in patients that do not present pathological signs, treatment with flutamide must be suspended.

Impaired renal function

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

Cardiovascular

Periodic sperm count should be considered in patients receiving chronic treatment with Flutamide who have not received medical or surgical castration. Flutamide administration may lead to elevated plasma testosterone and oestradiol levels in such patients, resulting in fluid retention. In severe cases this can lead to an increased risk of angina and heart failure. Therefore caution should be exercised in the use of Flutamide if cardiac disease is present.

Flutamide can exacerbate oedema or ankle swelling in patients prone to these conditions.

The increase in levels of oestradiol may predispose to thromboembolic events.

It has been reported in the literature that increased cardiovascular risk (myocardial infarction, cardiac insufficiency, sudden cardiac death) and the adverse effect on independent cardiovascular risk factors (serum lipoproteins, insulin sensitivity and obesity) may be linked to androgen deprivation with LHRH analogues in patients with prostate cancer. It must be evaluated whether the benefits of the combined androgen blockade compensate the potential cardiovascular risk in patients with risk factors. Patients treated whose signs or symptoms suggest the development of a cardiovascular disease must be monitored.

Effect on QT/QTc interval

The potential QT/QTc prolongation with flutamide has not been studied. 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) physician should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Flutamide

Endocrinology and metabolism

A decreased tolerance to glucose has been observed in males in treatment with combined androgen blockade. This may manifest as diabetes or a loss of glycaemic control in patients with pre-existing diabetes. Monitoring of the blood glucose and/or glycosylated haemoglobin (HbA1c) levels must be considered in patients who are in treatment with flutamide in combination with LHRH agonists.

Musculoskeletal/changes in bone density

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. The risk of bone fractures increases with the duration of combined androgen blockade. 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.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic consumers of alcohol and/or tobacco, a presumed or marked family history of osteoporosis or chronic use of medicinal products that can reduce bone mass such as anticonvulsants or corticosteroids, the combined androgen blockade can represent an additional risk. In these patients the risk and benefit must be weighed up carefully before starting the 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.

Flutamide is indicated for use only in male patients.

Contraceptive measures should be taken during treatment.

The tablets contain lactose. 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

There have been no interactions between flutamide and leuprorelin; nevertheless, in the combined therapy with flutamide and an LHRH agonist, the possible side effects of each medicinal product must be considered.

Increases in prothrombin time have been reported in patients receiving chronic treatment with oral anticoagulants (eg.warfarin) following initiation of flutamide monotherapy. Therefore, careful monitoring of prothrombin time is recommended and it may be necessary to adjust the dose of the anticoagulant if Flutamide is administered concomitantly with oral anticoagulants.

Concomitant administration of other potentially hepatotoxic drugs should be undertaken only after careful assessment of the benefit and risks. Given the known potential liver and renal toxicities of the product, it is important to avoid excessive alcohol consumption.

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-hydroxyflutamide.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Flutamide with medicinal products known to prolong 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, dofetillide, ibutillide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc ,should be carefully evaluated(see section 4.4).

4.6 Fertility, pregnancy and lactation

Flutamide is intended only 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 related to the anti-androgenic 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).

No studies have been conducted in pregnant or lactating women. Therefore, the possibility that flutamide Tablets may cause foetal harm if administered to a pregnant woman, 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 the effects on the ability to drive and use machines have been performed with Flutamide. However, possible undesirable effects such as fatigue, dizziness and confusion have been reported and may interfere with the ability to drive and use machines.

4.8 Undesirable effects

Monotherapy

The undesirable effects of flutamide most frequently reported are gynaecomastia and/or breast tenderness, sometimes accompanied by periods of galactorrhoea. These reactions often disappear with the suspension of treatment or reduction in dosage.

It has been proven that famotidine has a low cardiovascular risk potential, significantly less than that of diethylstilboestrol.

Combined therapy

The undesirable effects most frequently reported during combined treatment of famotidine with an LHRH agonist were hot flushes, reduced libido, erectile dysfunction, diarrhoea, nausea and vomiting. With the exception of diarrhoea, these are known undesirable effects of LHRH agonist alone, with a similar frequency.

The high rate of occurrence of gynecomastia observed with monotherapy with Famotidine decreased greatly in combined treatment. In clinical trials, no significant difference was observed in the rate of occurrence of gynecomastia between the placebo group and the group treated with famotidine and LHRH agonist.

The following convention has been utilised for the frequency classification:
Very common- (≥1in 10)
Common-(≥1in 100 to < 1 in 10)
Uncommon-(≥1in 1,000 to < 1 in 100)
Rare-(≥1in 10,000 to < 1 in 1,000)
Very rare – (< 1 in 10,000)
Not known- (cannot be estimated from the available data)

SOC	Monotherapy	Combination therapy with LHRH analog
Infections and infestations		
Rare	Herpes zoster	
Neoplasms benign ,malignant and unspecified (including cysts and polyps)		
Very rare	Neoplasm of the male breast*	

Blood and the lymphatic system disorders		
Rare		Anaemia, leucopenia, thrombocytopenia
Very Rare		Haemolytic anaemia, macrocytic anaemia , megalocytic anaemia, methaemoglobinaemia, sulfhaemoglobinaemia
Immune system disorders		
Rare	Lupus-like syndrome	
Metabolism and nutrition disorders		
Common	Increased appetite	
Rare	Anorexia	Anorexia
Very rare		Hyperglycaemia, aggravation of diabetes mellitus
Psychiatric disorders		
Common	Insomnia	
Rare	Anxiety, depression	Depression, anxiety
Nervous System Disorders		
Rare	Dizziness, headache	Drowsiness, confusion, nervousness, numbness
Eye Disorders		
Rare	Blurred vision	
Cardiac disorders		
Rare	Cardiovascular disorders	
Not known	QT prolongation (see sections 4.4 and 4.5)	
Vascular disorders		
Very common		Hot flushes
Rare	Hot flushes, Hypertension,	Hypertension

	lymphoedema	
Not known		Thromboembolism
Respiratory, thoracic and mediastinal disorders		
Rare	Interstitial pneumonitis, dyspnoea	
Very rare	Cough	Pulmonary symptoms (e.g. dyspnoea), Interstitial lung disease
Gastrointestinal disorders		
Very common		Diarrhoea, nausea, vomiting
Common	Diarrhoea, nausea, vomiting	
Rare	Non-specific abdominal disorders , Upset stomach, ulcer like-pain, heartburn, constipation , dyspepsia, colitis	Non-specific abdominal disorders, abdominal pain
Hepato-biliary disorders		
Common	Hepatitis	
Uncommon		Hepatitis
Rare	Liver function test Abnormalities (see section 4.4)	Hepatic dysfunction, Jaundice
Very rare		Cholestatic jaundice, hepatic encephalopathy, liver cell necrosis, hepatotoxicity with fatal outcome.
Skin and subcutaneous tissue disorders		
Rare	Urticaria, Pruritus, ecchymosis ,alteration of the hair growth pattern and loss of hair (head)	Rash

Very rare	Photosensitivity reactions	Photosensitivity reactions, erythema, ulcer, bullous eruptions, epidermal necrolysis
Musculoskeletal and connective tissue disorders		
Rare	Muscle cramps	Neuromuscular symptoms ,reduced bone mineral density, osteoporotic disorders, arthralgia, myalgia
Renal and urinary disorder		
Rare		Genitourinary tract symptoms, dysuria, changes in urinary frequency, change in urine colour to amber or yellow-green.
Reproductive system and breast disorders		
Very Common	Gynecomastia and/or breast pain ,breast tenderness, galactorrhoea	Decreased libido, impotence
Uncommon		Gynecomastia
Rare	Reversible increase of serum testosterone levels , Decreased libido Reduced sperm counts	
General disorders and administration site conditions		
Common	Somnolence ,Tiredness	
Rare	Oedema, asthenia , weakness, malaise, thirst, chest pain, hot flushes	Oedema, Injection site irritation
Investigations		
Common	Transient abnormal liver function	Changes in liver function
Rare		elevated blood urea nitrogen (BUN) values , Elevated serum creatinine values

*There have been a few cases reported of malignant breast neoplasms in male patients treated with famotidine. One of them consisted of the aggravation of a lump that had been detected previously, three or four months prior to commencing monotherapy with flutamide in a patient with benign prostatic hypertrophy. After the excision, a diagnosis was made of slightly differentiated ductal carcinoma. The other case consisted of gynaecomastia and a lump, observed, respectively, two to six months after the start of monotherapy with flutamide to treat an advanced prostate carcinoma. Nine months after the treatment began, the lump was removed and a moderately differentiated invasive ductal tumour was diagnosed in T4N0M0, G3 state.

Micronodular alterations of the body of breast can uncommonly occur.

An increase in serum testosterone is initially possible during monotherapy with flutamide; in addition, hot flushes and changes in hair character can occur.

Following the marketing of flutamide, cases of acute renal failure, interstitial nephritis, and myocardial ischemia have been reported with frequency unknown.

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 methaemoglobinaemia.

Clinical trials have been carried out with famotidine at doses of up to 1500 mg per day for periods up to 36 weeks without reports of severe undesirable effects. The undesirable effects reported were gynecomastia, breast sensitivity and some increases in SGOT.

The acute toxic dose of Flutamide in man has not been established. One patient survived after ingesting more than 5g as a single dose with no apparent adverse effects.

Since flutamide is an anilide compound, it has the theoretic potential of producing methaemoglobinaemia. Accordingly, a patient with acute intoxication may be cyanotic.

Management

If vomiting does not occur spontaneously it should be induced, provided that the patient is alert. Gastric lavage may be considered. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. General supportive measures are appropriate, including frequent monitoring of vital signs and close observation of the patient. Since flutamide is highly protein bound, dialysis may not be of any use as treatment for overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents, Anti-androgens, ATC code: L02BB01.

Mechanism of action

Flutamide is non-steroidal, high specific, orally active anti-androgenic agent. 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. The biological activity of oral flutamide is attributable to its pharmacologically active metabolite, hydroxyflutamide, which is believed to exert an anti-androgenic effect directly on the target tissues, either by inhibiting androgen uptake or by blocking cytoplasmic and nuclear binding of androgen.

Clinical efficacy and safety

In the clinical trial performed with flutamide linked to LHRH agonists as neoadjuvant therapy for locally confined prostate carcinomas, pre-radical surgery or radiotherapy, an increase in the survival rate has not been proven, although a decrease in the size of the tumour, a reduction in morbidity and surgical consequences and delays in the disease progression have been witnessed.

5.2 Pharmacokinetic properties

Absorption

Flutamide is rapidly and extensively absorbed and almost completely metabolised following oral administration.

Distribution

A high proportion of flutamide binds to plasma proteins (94-96%) as does its active metabolite (92-94%). The peak plasma concentration of hydroxyflutamide at steady state at the recommended therapeutic dose (250 mg t.i.d.) is approximately 1700 μg/L.

Biotransformation
The major metabolite is hydroxyflutamide, which has been demonstrated to possess potent anti-androgenic activity. Radiolabelled flutamide studies reveal a rapid and extensive conversion to its metabolites; at least 6 have been identified in the plasma up to 8 hours after administration.

Elimination
Approximately 45% of the administered dose is excreted in urine and 2% in faeces during the first two days.
The excretion and metabolism is essentially complete within two days. The elimination half-life in plasma is 5 to 6 hours in adults for flutamide and its main metabolite hydroxyflutamide and 8 hours in older people. The elimination half-life at steady-state is approximately 10 hours.

5.3 Preclinical safety data

The effects observed in oral repeat dose toxicology studies in the rat, dog and monkey were as expected for a potent anti-androgenic agent.

Studies have been performed in animals to determine the tolerance after repeated oral administration for a period of up to 6, 52 and 78 weeks in monkeys, rats and dogs, respectively. The oral doses administered daily reached 90 mg/kg in monkeys, 40 mg/kg in dogs and 180 mg/kg in rats, which corresponded to 1.5 to 18 times the dose used in humans. In addition to weight loss and anorexia, which occurred in all of the animal species, vomiting was observed in dogs and monkeys. The rest of the clinical observations did not reveal any anomalies.

Reductions in prostate gland and seminal vesicle weights were observed in all species and reduced testicular weights were observed in the rat and monkey. Histological changes characteristic of anti-androgenic activity were observed in all species and there was evidence of suppression of spermatogenesis.

In addition, an increase in the weight of the liver in rats and dogs and elevated transaminase levels in dogs without the corresponding morphological changes were observed. In rats only, the emergence of adenomas of the interstitial testicular cells linked to the medicinal product were observed (although they were not dose-dependent). This effect is related to the mechanism of action of flutamide and is species-specific. In a long-term study in rats, increases were found in the rate of occurrence of adenomas or carcinomas of the mammary gland related to the dose.

Mutagenicity :
No mutagenic potential was observed with flutamide in a variety of screening tests.

Reproduction toxicity:

The influence of flutamide on fertility and the development of the progeny has been studied in rats; additional teratogenicity studies have been performed in rabbits. The effects were related to the anti-androgenic actions of flutamide. These effects are not relevant to the clinical use of flutamide in prostate cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize Starch
Microcrystalline Cellulose
Sodium Lauryl Sulfate
Colloidal anhydrous silica
Magnesium Stearate

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store the tablets in the original package.

6.5 Nature and contents of container

PVC/aluminium blister strips in a cardboard carton
28, 56 and 84 tablets per pack

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited

11 Boumpoulinas

Nicosia

1060

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0207

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05/10/1999
Date of latest renewal: 11/10/2006

10 DATE OF REVISION OF THE TEXT

04/03/2019