1. Name of the medicinal product

FLUTAMIDE TABLETS 250 MG

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABEL CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Flutamide	USP	250.00 mg	0.00 %	250.000 mg	API
INACTIVE INGREDIENTS						
2.	Maize starch	BP	-	0.00%	270.000 mg	Diluent
3.	Dibasic calcium phosphate	BP	-	0.00 %	176.000 mg	Diluent
4.	Sodium starch glycolate	BP	-	0.00 %	16.000 mg	Disintegrant
5.	Povidone	BP	-	0.00 %	20.000 mg	Binder
6.	Isopropyl alcohol*	BP	-	0.00 %	0.050 ml	Solvent
7.	Magnesium stearate	BP	-	0.00 %	8.000 mg	Lubricant
8.	Purified talc	BP	-	0.00 %	16.000 mg	Glidant
9.	Croscarmellose sodium	BP	-	0.00 %	16.000 mg	Disintegrant
10.	Colloidal silicon dioxide	USP	-	0.00 %	8.000 mg	Glidant

* Evaporates during manufacturing, does not remain in final formulation.

3. Pharmaceutical form

Oral Tablet

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 tablet three 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 8 weeks prior to radiotherapy and continue for its duration, or for 12 weeks pre-prostatectomy.
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.
Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.
Impaired renal function: Flutamide should be administered with caution in patients with impaired renal function.
Cardiovascular: Periodic sperm counts 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. It can exacerbate oedema or ankle swelling in patients prone to these conditions.
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.

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 treatment 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 (e.g. warfarin) following initiation of flutamide monotherapy. Therefore careful monitoring of prothrombin time is recommended and it may be necessary to adjust the dose of 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 consumption of alcohol.
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.

4.6 Pregnancy and lactation

Flutamide is intended only for use in male patients. Contraceptive measures should be taken during treatment.
Flutamide may cause foetal harm when administered to a pregnant woman. 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.

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. 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

Blood and lymphatic system disorders:
Combination therapy with LHRH analog: Anaemia, leucopenia, thrombocytopenia, Haemolytic anaemia, megalocytic anaemia, methaemoglobinaemia, sulfhaemoglobinaemia, macrocytic anaemia.
Immune system disorders: Lupus-like syndrome.
Metabolism and nutrition disorders:
Monotherapy: Increased appetite, Anorexia.
Combination therapy with LHRH analog: Hyperglycaemia, aggravation of diabetes mellitus, Anorexia.
Psychiatric disorders
Monotherapy: Insomnia, Anxiety, depression.
Combination therapy with LHRH analog: Depression, anxiety.
Nervous system disorders
Monotherapy: Dizziness, headache.
Combination therapy with LHRH analog: Numbness, confusion, nervousness, drowsiness.
Vascular disorders

Monotherapy: Hot flushes, hypertension, lymphedema.
Combination therapy with LHRH analog: Hot flushes, Hypertension, Thromboembolism.
Respiratory, thoracic and mediastinal disorders:
Monotherapy: Interstitial pneumonitis, dyspnea, Cough.
Combination therapy with LHRH analog: Pulmonary symptoms (e.g. dyspnoea), interstitial lung disease.
Gastrointestinal disorders:
Monotherapy: Nausea, vomiting, diarrhea, Non-specific abdominal disorders, constipation, ulcer-like pain, dyspepsia, colitis, upset stomach, heartburn.
Combination therapy with LHRH analog: Non-specific abdominal disorders, abdominal pain.

4.9 Overdose

Symptoms: Clinical trials have been carried out with flutamide at doses of up to 1500 mg per day for periods of up to 36 weeks without reports of severe undesirable effects. The undesirable effects reported were gynaecomastia, 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 5 g 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 anatagonists and related agents, Anti-androgens, ATC code: L02BB01
Mechanism of action: Flutamide is a non-steroidal, highly 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.

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 the 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 the treatment of prostate cancer.

6. Pharmaceutical particulars

6.1 List of Excipients

- Maize starch
- Dibasic calcium phosphate
- Sodium starch glycolate
- Povidone

- Isopropyl alcohol*
- Magnesium stearate
- Purified talc
- Croscarmellose sodium
- Colloidal silicon dioxide.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

4 x 21 Tablets Alu-PVC Blister Pack in printed and laminated carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

West Coast Pharmaceutical Works Ltd, Ahmedabad

8. Marketing authorisation number(s)

Not applicable.

9. Date of first authorisation/renewal of the authorisation

Not applicable.

10. Date of revision of the text

October, 2016