

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Prostamide Tablets 250 mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prostamide Tablets contain Flutamide 250mg.

Amount of lactose per tablet: 221.7 mg

For a full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM

Tablets.

Yellow biconvex tablets marked 'FT' score '250' on one side with a 'G' on the reverse.  
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Prostamide 250mg are indicated for the treatment of advanced prostatic carcinoma in which suppression of testosterone effects is indicated. Prostamide 250mg 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. Prostamide 250mg may also be used in surgically castrated patients.

### 4.2 Posology and method of administration

Adults and the Elderly: One tablet three times daily. The tablets are to be taken preferably after meals. When Prostamide are used as initial treatment with an LHRH agonist, a reduction in severity of the flare reaction may be achieved if treatment with Prostamide is initiated before the LHRH agonist. Consequently, it is recommended that treatment with Prostamide should commence at least three days before the LHRH agonist.

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

Prostamide 250 mg tablets should be administered with caution in patients with impaired renal function.

### 4.3 Contraindications

Prostamide 250mg are contraindicated in patients with known hypersensitivity to any of their components.

## 4.4 Special warnings and precautions for use

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

Hepatic injury: There have been reports of elevated serum transaminase levels, cholestatic jaundice, hepatic necrosis and hepatic encephalopathy associated with Prostamide treatment. The hepatic effects were usually reversible following discontinuation of Prostamide. 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 Prostamide therapy. Treatment with Prostamide 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.

Liver function tests should be performed at the first sign or symptom of hepatic dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained “flu-like” symptoms). Flutamide-induced hepatotoxicity usually recovers with dose reduction or drug withdrawal, but fatalities have been reported (see section 4.8).

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

Prostamide 250 mg tablets should be administered with caution in patients with impaired renal function.

Periodic sperm counts should be considered in patients receiving chronic treatment with Prostamide who have not received medical or surgical castration. Prostamide administration tends to elevate plasma testosterone and oestradiol levels in such patients. This may be associated with fluid retention and therefore caution should be exercised in the use of Prostamide if cardiac disease is present.

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 Prostamide. 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.

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

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

Prostamide is indicated only for use in male patients.

## 4.5 Interaction with other medicinal products and other forms of interaction

Increases in prothrombin time have been reported in patients receiving chronic treatment with warfarin following initiation of Prostamide monotherapy. It may be necessary to adjust the dose of anticoagulant if Prostamide is administered concomitantly with warfarin.

Avoid concomitant administration of potentially hepatotoxic drugs. Avoid excessive alcohol consumption.

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

4.6 Fertility, pregnancy and lactation

No studies have been conducted in pregnant or lactating women. In animal studies, reproductive toxicity was related to the antiandrogenic activity of this compound. See Section 5.3.

4.7 Effects on ability to drive and use machines

Possible undesirable effects such as tiredness and dizziness may interfere with 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

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.
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***

<b>SOC</b>	<b>Frequency</b>	<b>Reactions</b>
Blood and lymphatic system disorders	Rare	Anaemia, leukopenia, thrombocytopenia, oedema.
	Very rare	Haemolytic anaemia, macrocytic anaemia, methemoglobinaemia, sulfhemoglobinaemia
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

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

## 4.9 Overdose

In animal studies with Prostate alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia and/or lacrimation, anorexia, tranquilisation, emesis and methaemoglobinaemia.

The acute toxic dose of Prostate in man has not been established. One patient survived after ingesting more than 5g as a single dose, with no apparent adverse effects. Since Prostate is an anilide compound, it has the theoretic potential of producing methaemoglobinaemia. Accordingly, a patient with acute intoxication may be cyanotic. If vomiting does not occur spontaneously it should be induced, provided that the patient is alert. General supportive measures are appropriate, including frequent monitoring of vital signs and close observation of the patient. Since Prostate is highly protein bound, dialysis may not be of any use as treatment for overdose.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Anti-Androgens, ATC - Code L02 B B01

Prostate 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 Prostate treatment. The biological activity of oral Prostate 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

Prostate is rapidly and extensively absorbed and almost completely metabolised following oral administration. The major metabolite is hydroxyflutamide, which has been demonstrated to possess potent antiandrogenic activity. The elimination half life in plasma is 5 to 6 hours for Prostate and its main metabolite hydroxyflutamide. The peak plasma concentration of hydroxyflutamide at steady state at the recommended therapeutic dose (250mg t.i.d.) is approximately 1700µg/L and the elimination half-life at steady-state is approximately 10 hours. The drug is excreted mainly in the urine, with 4.2% of the dose excreted in the faeces over 72 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. 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.

The influence of Prostate 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 antiandrogenic actions of Prostate. These effects are not relevant to the clinical use of Prostate in the treatment of prostate cancer.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose  
Lactose monohydrate  
Pre-gelatinised maize starch  
Sodium laurilsulfate  
Colloidal anhydrous silica  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

4 years.

### **6.4 Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and contents of container**

Prostamide are packaged either in PVC/aluminium blister packs or in polypropylene pots with polyethylene caps (with optional polyethylene ullage filler), containing 20, 21, 30 50, 60, 84, 100, 105, 250 or 10\*21 tablets.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Generics (UK) Limited  
t/a Mylan  
Station Close  
Potters Bar  
Hertfordshire EN6 1TL  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 405/35/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 5<sup>th</sup> February 1999

Date of last renewal: 31<sup>st</sup> July 2006

## **10 DATE OF REVISION OF THE TEXT**

November 2010