Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Drogenil 250mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains flutamide 250mg.

Excipients: also includes lactose monohydrate, 222mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Pale yellow round, biconvex tablets with a score on one side and the SP logo on the other.
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

Treatment of advanced prostatic carcinoma 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 form of hormonal manipulation or in patients who cannot tolerate such treatment.

As a component of the treatment used in the management of locally confined B2−C2 (T2b-T4) prostatic carcinoma, Drogenil Tablets are also indicated to reduce tumour volume, to increase tumour control and to extend the disease-free interval.

4.2 Posology and method of administration

Dosage : One 250mg tablet three times daily at 8 hour intervals.

Route of Administration : Oral

When used as an 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 is introduced before rather than concomitantly with the agonist. It is, therefore, recommended that flutamide one tablet three times daily should be started simultaneously or 24 or more hours prior to initiation of the LHRH agonist and continued thereafter at the same dose.

In the management of locally confined prostatic carcinoma, the recommended dosage is one 250mg tablet three times a day at eight-hour intervals. If an LHRH agonist is part of the treatment regimen, Drogenil should be started simultaneously or 24 hours prior to initiation of the LHRH agonist. Administration of Drogenil should begin eight weeks prior to radiation therapy and continue through the course of radiation therapy.

Dosage adjustment in renal or liver insufficiency : In patients with impaired liver function, long-term treatment with flutamide should only be administered after careful assessment of the individual benefits and risks.

Monitoring advice : Flutamide is highly protein bound and will not be removed by dialysis.

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

Initiation of treatment should be under the direction of a specialist. Subsequently, patients should be kept under regular surveillance with particular attention to effects on liver function and spermatogenesis in those patients without orchidectomy.

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 necrosis, and hepatic encephalopathy have been reported with the use of flutamide, periodic liver function tests should be considered. 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 four months and then periodically or when first symptom/sign 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. (See section 4.8).

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.

In addition, in patients who have not received medical or surgical castration periodic sperm count determinations may be considered during long-term treatment. Flutamide administration tends to elevate plasma testosterone and estradiol 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 in caution in the presence of cardiovascular disease. Flutamide can exacerbate edema or ankle swelling in patients prone to these conditions.

The increase in levels of oestradiol may render the patient more susceptible to thromboembolism.

Patients with latent or actual G-6-P deficiency may develop methaemoglobinaemia.

Flutamide is excreted mainly through the kidney. Caution is advised in patients with impaired renal function. Dosage may require adjustment in patients with renal insufficiency. Elevated serum creatinine levels have been reported.

Drogenil is indicated for use only in male patients.
Contraceptive measures should be taken during treatment.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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 tablets 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 long-term 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 is administered concomitantly with oral anticoagulants. Flutamide may delay the metabolism of steroids.

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

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.

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 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

Flutamide is intended only for use in male patients. Contraceptive measures should be taken during treatment.

Flutamide may cause fetal harm when administered to a pregnant woman. In animal studies, the reproductive toxicity of flutamide was associated with 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 fetuses of rats at the two higher doses. Feminization 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 may cause fetal 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 Drogenil.
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

Monotherapy: In clinical studies, the most frequently reported adverse reactions to Drogenil Tablets are gynecomastia and/or breast tenderness, sometimes accompanied by galactorrhea. These reactions usually disappear upon discontinuation of treatment or reduction in dosage.

Drogenil Tablets demonstrate a low potential for cardiovascular liability, and when compared to diethylstilbestrol this liability has been shown to be significantly lower.

Combination therapy: In clinical studies, the most frequently reported adverse effects experienced during combination therapy of Drogenil Tablets with LHRH agonist were hot flushes, decreased libido, impotence, diarrhoea, nausea and vomiting. With the exception of diarrhoea, these adverse experiences are known to occur with LHRH agonist alone, and at comparable frequency. In clinical trials, no significant difference in gynecomastia incidence was observed between the placebo and the flutamide-LHRH agonist treatment groups.

Table 1. Treatment related undesirable effects
Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very rare (<1/10,000) and not known (cannot be estimated from the available data).

BODY SYSTEM	**DROGENIL**	**DROGENIL PLUS LHRH**
Infections and infestations		
Rare	Herpes zoster	
Neoplasms benign and malignant (including cysts and polyps)		
Very rare:	Male breast neoplasm*	Male breast neoplasm*
Blood and the lymphatic system disorders		
Rare	Edema, ecchymoses, lymphedema	Anemia, leucopenia, thrombocytopenia
Very Rare:		Edema, hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, megalocytic anemia

Immune system disorders		
Rare	Lupus-like syndrome	
Metabolism and nutrition disorders		
Common: Rare Very rare	Increased appetite Anorexia	 Anorexia Hyperglycemia, aggravation of diabetes mellitus
Psychiatric disorders		
Common Rare	Insomnia Anxiety, depression	 Depression, anxiety
Nervous System Disorders		
Common: Rare	Insomnia Dizziness, headache	 Drowsiness, confusion, nervousness, numbness
Eye Disorders		
Rare	Blurred vision	
Respiratory, thoracic and mediastinal disorders		
Very rare:		Lung symptoms (e.g. dyspneoa) Interstitial lung disease
Gastrointestinal disorders		
Very common Common: Rare:	 Diarrhea, nausea, vomiting Non-specific abdominal disorders, upset stomach, ulcer-like pain, heartburn, constipation	Diarrhea, nausea, vomiting Unspecified gastrointestinal disorders
Hepato-biliary disorders		
Common Uncommon Rare: Very rare:	Hepatitis	 Hepatitis Jaundice Cholestatic jaundice, hepatic encephalopathy, hepatic necrosis, cases of death following severe hepatic injury.
Skin and subcutaneous tissue disorders		
Rare Very rare	Pruritus, ecchymoses Photosensitivity reactions	Rash Photosensitivity reactions, erythema, ulcerations, bullous eruptions, epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders		
Rare		Neuromuscular symptoms
Renal and urinary disorder		
Rare Very rare:		Genitourinary tract symptoms Change in urine colour to amber or yellow-green
Reproductive system and breast disorders		
Very Common: Uncommon Rare	Gynecomastia and/or breast tenderness, galactorrhea Decreased libido Reduced sperm counts	Decreased libido, impotence, Gynecomastia

General disorders and administration site conditions		
Common: Rare	Tiredness Headache, weakness, malaise, thirst, chest pain, edema	 Injection site irritation and rash, edema
Investigations		
Common: Rare	Transient abnormal liver function and Hepatitis	 Changes in liver function, elevated blood urea nitrogen (BUN), Elevated serum creatinine
Vascular disorders		
Very common Rare Not known	Hot flushes	Hot flushes Hypertension Thromboembolism

* Two reports of malignant male breast neoplasms in patients being dosed with Drogenil have been reported. One involved aggravation of a pre-existing nodule which was first detected three to four months before initiation of Drogenil monotherapy in a patient with benign prostatic hypertrophy. After excision, this was diagnosed as a poorly differentiated ductal carcinoma. The other report involved gynecomastia and a nodule noted two and six months, respectively, after initiation of Drogenil 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 T4NOMO, G3, no metastases had advanced.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

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

Clinical trials have been conducted with flutamide Tablets or Capsules 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 gynecomastia, breast tenderness and some increases in SGOT.

The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established. Since flutamide is highly protein bound, dialysis may not be of any use as treatment for overdose. As in the management of overdose 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.

One patient survived after taking more than 5g as a single dose - no adverse effects were observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, ATC Code: GO3H A.

Flutamide is an anilide, nonsteroidal oral antiandrogen. In animal studies flutamide demonstrates potent antiandrogenic effects. It exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding in target tissues. When flutamide is given in combination with surgical or medical castration, suppression of both testicular and adrenal androgen activity is achieved.

5.2 Pharmacokinetic properties

Drongenil is well absorbed following oral ingestion. Studies with radiolabeled flutamide show rapid and extensive conversion to its metabolites which are detectable in plasma up to 8 hours post dosing. Approximately 45% of the administered dose is excreted in urine and 2% in faeces during the first two days. Metabolism removes the radiolabel resulting in apparent slowing of excretion due to retention of the label as tritiated water. Thus excretion and metabolism is essentially complete within two days.

5.3 Preclinical safety data

Preclinical safety data: Animal studies to determine tolerance after repeated administration have been performed in monkeys for up to 6 weeks, in rats for up to 52 weeks and in dogs for up to 78 weeks. The daily administered oral doses were up to 90mg/kg in monkeys, up to 40mg/kg in dogs and up to 180mg/kg in rats, corresponding to 1.5 to 18 fold of the dose used in humans. In addition to weight loss and anorexia which occurred in all animal species, vomiting was observed in dogs and monkeys. All other clinical findings showed no abnormalities. The autopsy finding revealed a reduced size of the prostate, testicles and seminal vesicles with suppressed spermatogenesis which corresponded to the antiandrogenic effect of flutamide. In addition, an increase in the organ weight of the liver in rats and dogs, and increased transaminase levels in dogs were observed without corresponding morphological changes. In rats only, the occurrence of drug-related (but not dose-dependent) adenomas of testicular interstitial cells was observed. This effect is related to the mechanism of action of flutamide and is species-specific. In a long-term study in rats, dose-related increases in mammary gland adenomas or carcinomas were observed.

Mutagenicity: In a range of screening tests flutamide did not show any mutagenic potential.

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 antiandrogenic 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
Sodium laurilsulfate
Microcrystalline cellulose
Maize starch
Silica gel
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters consisting of 10 micron amber PVC film on 10 micron aluminium foil with vinyl heat seal coating, in a cardboard carton. Blister strips of 21 tablets, four strips per pack and blister strips of 10 tablets, 10 strips per pack. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1286/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th November 1990

Date of last renewal: 22nd March 2007

10 DATE OF REVISION OF THE TEXT

April 2016