Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flutamid Stada 250 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flutamide 250 mg

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pale yellow round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of advanced prostatic carcinoma in which suppression of testosterone effects is indicated. Flutamid Stada may be used as initial treatment in combination with LHRH agonists or as adjunctive therapy in patients, already receiving LHRH agonist therapy. Flutamid Stada may also be used in surgically castrated patients.

4.2 Posology and method of adminstration

Adults and Elderly: One tablet three times daily. The tablets should be taken preferably after meals.
When Flutamid Stada tablets are used as initial treatment with an LHRH agonist, a reduction in severity of the flare reaction may be achieved if treatment with Flutamid Stada is initiated before the LHRH agonist. Consequently, it is recommended that treatment with Flutamid Stada should commence at least 3 days before the LHRH agonist.

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

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

4.3 Contraindications

Flutamid Stada is contraindicated in patients who are hypersensitive to flutamide or any component of the product.
For patients with severe liver impairment (Child Pugh C) the use of flutamide is also contraindicated.

4.4 Special warnings and precautions for use

In patients with pre-existing liver dysfunction the hazard of flutamide-induced hepatic injury may be increased. Therefore, in these patients long-term treatment with flutamide should only be initiated after careful assessment of the individual benefits and 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 there have been occasional reports of fatalities following severe hepatic injury in patients receiving the drug. Periodic liver function tests must be performed before initiation

and during treatment especially in patients receiving long-term treatment with flutamide.

Appropriate laboratory testing should be done at the first symptom/sign of liver dysfunction (e.g. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained “flu-like” symptoms). If the patient has laboratory evidence of liver injury or jaundice, in the absence of biopsy confirmed liver metastases, flutamide therapy should be discontinued or dosage reduced.

Flutamide should be administered with caution in patient with impaired renal function.

Periodic sperm counts should be considered in patients receiving chronic treatment with flutamide who have not received medical or surgical castration. Flutamide 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 flutamide if cardiac disease is present.

In patients developing a flutamide refractory stage of prostate cancer, flutamide withdrawal may provide short-term (months) therapeutic benefit in about 30% of the patients. Cessation of flutamide for at least 4 weeks is needed to assess flutamide withdrawal response in terms of reduced PSA levels.

4.5 Interaction with other medicinal products and other forms of interaction

Increases in prothrombin time have been reported in patients treated with warfarin. Adjustment of the dose may be necessary when used concomitantly with warfarin.

4.6 Pregnancy and lactation

Not relevant due to the indication.

4.7 Effects on ability to drive and use machines

Patient should be advised that initial sedative effects may interfere with driving and the operation of machinery.

4.8 Undesirable effects

It has to be noted that published frequencies of adverse events are not consistent and/or comprehensively indicated in every publication.

Flutamide monotherapy

The most commonly reported adverse effects are hot flushes, nausea, diarrhoea, liver disturbances, and gynecomastia. Mild gynecomastia was observed in 57%, moderate gynecomastia in 36%, and massive gynecomastia in 8% of patients. The following adverse drug reactions were reported although their incidence rate in part greatly varies among different publications.

Organ systems	**Very common >1/10**	**Common >1/100, <1/10**	**Uncommon >1/1,000, <1/1,000**	**Rare >1/10,000, <1/1,000**	**Very rare <1/10,000**
Infections and infestations			Urinary tract infections		
Neoplasms benign and malignant			Nodular alteration of the breast		Malignant male breast neoplasms
Blood and the lymphatic system disorders		Leukopenia, thrombocytopenia, haemolytic anemia, macrocytic anemia,			Sulfhemoglobinemia, neutropenia

		methemoglobinemia			
Endocrine disorders			Initially reversible increase of serum testosterone		
Psychiatric disorders				Anxiety, depression, nervousness, manic-type syndrome	
Nervous system disorders			Dizziness, insomnia, headache		
Eye disorders				Blurred vision	
Cardiac disorders				Myocardial ischemia	
Vascular disorders		Thromboembolism		Oedema, lymph oedema, hypertension	
Respiratory, thoracic and mediastinal disorders				Chest pain	Interstitial pneumonitis, hypoxemia
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Increased appetite		Anorexia, constipation, dyspepsia, ulcer-like pain and heartburn, lymphocytic colitis	Ischemic colitis (1 case)
Hepato-biliary disorders	Elevated liver transaminases	Hepatotoxicity		Abnormalities in liver function tests, cholestatic hepatitis with jaundice	Hepatic failure
Skin and subcutaneous tissue disorders	Initially flushes, alteration of the hair growth pattern			Photosensitivity erythema, ulceration, bullous eruptions, papulovesicular eruptions, epidermal necrolysis, ecchymoses, herpes zoster, pruritus and lupus-like syndrome	
Musuloskeletal, connective tissue and bone disorders				Muscle cramps, bone pain	Systemic lupus erythematosus (1 case)
Renal and			Transient	Greenish or	Acute renal failure (1

urinary disorders			elevations of blood urea nitrogen (BUN) and elevated serum creatinine levels without reports of impaired renal function	dark yellow discolouration of the urine	case)
Reproductive system and breast disorders	Gynecomastia breast tenderness, sometimes accompanied by galactorrhoea			Decreased libido, reduced sperm counts	
Congenital and familial/genetic disorders					Teratogenic data is lacking for humans. Animal data indicate that a decreased survival time, feminization of male fetuses, slight increase in minor skeletal malformations
General disorders	Insomnia and tiredness		Weakness, malaise, thirst		

These effects are not necessarily drug-related and may be due to the underlying clinical condition. In most cases the reactions have not been of sufficient severity to necessitate either withdrawal of flutamide or reduction in the dosage.

Very rarely, serious adverse reactions in the form of hepatic injury (see Special Warnings and Precautions) have occurred, in particular in patients with pre-existing liver dysfunction. Hepatotoxicity may include elevated serum transaminases, jaundice, hepatic encephalopathy, fulminant hepatitis, cholestatic hepatitis, hepatic failure and hepatic necrosis.

Combination therapy (flutamide plus LHRH agonist)
In combination therapy the quality of adverse reactions is largely comparable to that under monotherapy. Their frequency may be comparable to that under monotherapy or may be at variance. However, reports on detailed incidence rates under combination therapy are scarce.

The most commonly reported adverse effects were hot flushes (61%), loss of libido (36%), impotence (33%), nausea or vomiting (14%), and diarrhea (13.6%). However, only diarrhea occurred more frequently in flutamide-treated patients compared with those treated with the LHRH-agonist alone. The incidence of gynecomastia observed with flutamide monotherapy was reduced in combination therapy.

The following table compiles those adverse drug reactions which differ in their incidence rates greatly from monotherapy.

Organ systems	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
Gastrointestinal disorders	loss of appetite, vomiting/nausea and diarrhoea				
Skin and subcutaneous tissue disorders	flushes, decreased libido, impotence, diarrhoea, nausea and vomiting				
Reproductive system and breast disorders		gynecomastia, loss of sexual desire, decrease in penile erectile potency, decrease in sexual satisfaction			

4.9 Overdose

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. No adverse effects were seen.

Since flutamide is an anilide it has the theoretic potential of producing methaemoglobinaemia which means that 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 observations of the patient. Flutamide is highly protein bound and will not be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-androgens
ATC-code: L02BB01

Flutamide is a nonsteroidal substance (derivative of anilide) with antiandrogen properties. Flutamide acts on the cellular level. It exerts its antiandrogenic action by inhibiting androgen (mainly testosterone) uptake and/or by inhibiting nuclear binding in target tissues. By combined treatment with an antiandrogen such as flutamide and an LHRH-agonist so-called total androgen block, less androgen effect in the tumour is obtained compared with the LHRH-agonist used as monotherapy. This is caused by flutamide blocking the peripheral androgen receptor and thereby preventing androgens which are produced both in the adrenal gland and testis to affect the target tissues. Patients in an advanced stage with small tumour burden will benefit most from the treatment.

Concomitant treatment with an LHRH-agonist also prevents a flare-up reaction of the disease which occurs during the first month of treatment with the LHRH-agonist caused by an initial elevation of the testosterone levels with a significant increase of prostate specific antigen (PSA).

5.2 Pharmacokinetic properties

The pharmacokinetic characteristics of flutamide used as monotherapy are incompletely studied. Peak serum concentration is obtained after about 1-2 hours. The plasma protein binding is about 95%. Flutamide is extensively

metabolised. One hour after dosing only 2.5% of given dose consists of unchanged flutamide. The major metabolite in plasma is alphahydroxyflutamide which is pharmacologically active and contributes to the pharmacological effect to a higher degree than the main substance. About 30 times higher plasma concentration of the active metabolite is achieved. The terminal plasma half-lifes of the flutamide and the active metabolite are about 8 hours and 9 hours respectively. After repeated dose the steady-state concentration of flutamide is obtained within about 4 days. Flutamide is mainly eliminated by metabolism and the metabolites are excreted via urine. Only about 5% is excreted via the faeces.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize starch
Sodium lauryl sulphate
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips with 21, 50, 84, 90, 100, 105 or 200 tablets in each box.

Not all pack sizes may be marketed in all countries.

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

STADA Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel

Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 July 2002

10 DATE OF REVISION OF THE TEXT

February 2005