

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flutamid Stada 250 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flutamide 250 mg

Excipient with known effect:
Lactose monohydrate 220 mg.

For the full list of excipients, see section 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 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 administration

Posology

Adults and older people

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.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- For patients with severe liver impairment (Child Pugh C) the use of flutamide is also contraindicated.

4.4 Special warnings and precautions for use

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 tablets or capsules, 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 tablets or capsules.

Appropriate laboratory liver function tests should be done for every patient once monthly for the first 4 month and then periodically or when first sign/symptoms of liver dysfunction (e.g. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms) occur. Flutamide tablet or capsule 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.

Flutamide is indicated only for use in male patients.

Contraceptive measures should be taken during treatment.

Flutamide should be used with caution in patients with impaired renal function.

Flutamide may lead to elevated testosterone and estradiol plasma 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 with caution in the presence of cardiovascular disease. Flutamide can exacerbate oedema or ankle swelling in patients prone to these conditions.

An increase in estradiol levels may predispose to thromboembolic events.

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) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating flutamide.

Men who receive long-term flutamide treatment in the absence of pharmaceutical or surgical castration, should have sperm counts checked at regular intervals.

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.

Patients with rare hereditary galactose-intolerance, total lactose-deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 or capsules administered with an LHRH agonist, the possible adverse effects of each product must be considered.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of flutamide with medicinal products known to prolong the 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,

dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Increases in prothrombin time have been noted in patients receiving oral anticoagulants therapy after flutamide tablets or capsules was initiated. Therefore close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when flutamide tablet or capsule is administered concomitantly with oral anticoagulants.

Cases of increased theophylline plasma concentrations have been reported.

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.

4.6 Fertility, pregnancy and lactation

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

Flutamide tablets or capsules may cause foetal 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 foetuses 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 tablets or capsules 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. 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

The most frequently reported adverse reactions to flutamide tablets or capsules are gynecomastia and/or breast tenderness, sometimes accompanied by galactorrhoea. Mild gynecomastia was observed in 57 %, moderate gynecomastia in 36 % and massive gynecomastia in 8 % of patients. These reactions usually disappear upon discontinuation of treatment or reduction in dosage.

Flutamide tablets or capsules demonstrates a low potential for cardiovascular liability, and when compared to diethylstilbestrol this liability has been shown to be significantly lower.

Combination Therapy

The most frequently reported adverse effect experienced during combination therapy of flutamide tablets or capsules with an LHRH agonist were hot flushes (61 %), decreased libido (36 %), impotence (33 %), diarrhoea (13.6 %), nausea and vomiting (14 %). With the exception of diarrhoea, these adverse experiences are known to occur with LHRH agonists alone, and at comparable frequency.

The high incidence of gynecomastia observed with flutamide tablets or capsules monotherapy was markedly lower in combination therapy. In clinical trials, no significant difference in gynecomastia incidence was observed between the placebo- and the flutamide tablets or capsules- LHRH agonist treatment groups.

The following convention has been utilised for the classification of frequency: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1.000$ to $< 1/100$), Rare ($\geq 1/10.000$ to $< 1/1.000$) and Very rare ($< 1/10.000$), and not known (cannot be estimated from the available data).

SOC	Monotherapy	Combination-therapy with LHRH analog
<i>Investigations</i>		
Common:	Transient abnormal liver function	
Rare:		Elevated blood urea values, elevated serum creatinine values
<i>Blood and lymphatic system disorder</i>		
Rare:	Lymphoedema	Anaemia, leukopenia, thrombocytopenia
Very rare:		Haemolytic anaemia, megalocytic anaemia, methemoglobinemia, sulphaemoglobinaemia
<i>Nervous system disorders</i>		
Rare:	Dizziness, headache	Numbness, confusion, nervousness
<i>Eye disorders</i>		
Rare:	Vision blurred	
<i>Respiratory, thoracic and mediastinal disorders</i>		
Very rare:		Lung symptoms (e.g. dyspnoea), interstitial lung disease)
<i>Gastrointestinal disorders</i>		
Very common		Diarrhoea, nausea, vomiting
Common:	Diarrhoea, nausea, vomiting	
Rare:	Non-specific abdominal disorders, heart burn, constipation	Non-specific abdominal disorders
<i>Renal and urinary disorders</i>		
Rare		Urogenital symptoms
Very rare		Amber or greenish-yellow discoloration of urine
<i>Skin and subcutaneous tissue disorders</i>		
Rare:	Pruritus, ecchymoses	Rash

Very rare:	Photosensitivity reactions	Photosensitivity reactions, erythema, ulcers, epidermal necrolysis
<i>Musculoskeletal and connective tissue disorders</i>		
Rare:		Neuromuscular symptoms
<i>Metabolism and nutrition disorders</i>		
Common:	Increased appetite	
Rare:	Anorexia	Anorexia
Very rare:		Hyperglycaemia, aggravation of diabetes mellitus
<i>Infections and infestations</i>		
Rare:	Herpes zoster	
<i>Neoplasm benign, malignant and unspecified (including cysts and polyps)</i>		
Very rare:	Neoplasm of the male breast*	
<i>Cardiac disorders</i>		
Not known:	QT prolongation (see sections 4.4 and 4.5)	
<i>Vascular disorders</i>		
Very common:		Hot flushes
Rare:	Hot flushes	Hypertension
Not known:		Thromboembolism
<i>General disorders and administration site conditions</i>		
Common:	Tiredness	
Rare:	Oedema, weakness, malaise, thirst, chest pain	Oedema,
<i>Immune system disorders</i>		
Rare:	Lupus-like syndrome	
<i>Hepatobiliary disorders</i>		
Common:	Hepatitis	
Uncommon:		Hepatitis
Rare:		Hepatic dysfunction, Jaundice
Very rare:		Cholestatic icterus, hepatic encephalopathy, liver cell necrosis, hepatotoxicity with fatal outcome
<i>Reproductive system and breast disorders</i>		
Very common:	Gynecomastia and/or breast pain, galactorrhoea	Decreased libido, Impotence.

Uncommon:		Gynaecomastia
Rare:	Decreased libido, decreased sperm production	
Psychiatric disorders		
Common:	Insomnia	
Rare:	Anxiety, depression	Depression, anxiety

*Few reports of malignant male breast neoplasms in patients being dosed with flutamide tablets have been reported. One involved aggravation of a pre-existing nodule which was first detected three to four months before initiation of flutamide 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 flutamide 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, stage T4N0M0, G3.

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 national reporting system listed in Appendix V.

4.9 Overdose

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

Clinical trials have been conducted with flutamide tablets or capsules in doses up to 1,500 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 tablets or capsules ordinarily associated with symptoms of overdose or considered to be life-threatening has not been established. Since flutamide tablets or capsules is highly protein bound, dialysis may not be of any use for overdose treatment. As in the management of overdosage 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.

If vomiting does not occur spontaneously it should be induced, provided that the patient is alert.

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 of 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-lives 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 marked.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed nationally]

10. DATE OF REVISION OF THE TEXT

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