Drug Monograph

A - Drug Name

flutamide

SYNONYM(S): SCH 13521

COMMON TRADE NAME(S): Euflex® (Merck)

back to top

B - Mechanism of Action and Pharmacokinetics

Flutamide is a non-steroidal antiandrogen that inhibits androgen uptake and/or nuclear binding of androgen in target tissues. When used as monotherapy, it causes a gradual increase in plasma testosterone due to blockage of feedback inhibition of the hypothalamus and pituitary by testosterone. The increase does not occur when flutamide is used in combination with an LHRH agonist, nor in a previously orchidectomized patient

Absorption	Oral: Rapid and almost complete. With 250mg tid dosing, steady state is reached after the fourth dose.	
Distribution	In animal studies, accumulation occurs preferentially in the prostate.	
	Cross blood brain barrier?	No information found.
	PPB	94-96% (flutamide), 92-94% (active metabolite)
Metabolism	Rapid and extensive	
	Active metabolites	2-hydroxyflutamide
	Inactive metabolites	yes
Elimination	Primarily in urine	
	Feces	4% of the dose within 72 hours
	Urine	28% in 24 hours

Half-life	10 hours (active metabolite)

back to top

C - Indications and Status

Health Canada Approvals:

- Metastatic prostate cancer (Stage D2) in conjunction with LHRH agonist or orchiectomy
- Stage B2 or C prostate cancer prior to or during radiation treatment in combination with LHRH agonist.

back to top

D - Adverse Effects

Emetogenic potential: Not applicable

Extravasation Potential: Not applicable

The following table contains adverse effects reported in combination use with a LHRH agonist.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**	
Cardiovascular	Arterial thromboembolism (rare)		D
	Cardiotoxicity (rare)		D
	Hypertension (1%)		D
	Venous thromboembolism (rare)		D
Dermatological	Photosensitivity (may be severe)	E	
	Rash (3%) (may be severe)	E	
Gastrointestinal	Anorexia (4%)	E	
	Diarrhea (12%)	E	
	Nausea (or vomiting - 11%)	I	
General	Edema (4%)		D
Hematological	Hemolysis (rare)	E	D
	Myelosuppression (6%) (mild, including anemia)	E	
	Other (methemoglobinemia - rare)	E	
Hepatobiliary	↑ LFTs (may be severe)		D
Immune	Autoimmune disorder (Lupus-like syndrome - rare)	E	
Injection site	Injection site reaction (3%) (with LHRH agonist)	I	

Metabolic / Endocrine	Glucose intolerance		E D	
Neoplastic	Secondary malignancy (breast cancer - rare)			L
Nervous System	Cognitive disturbance (1%)		D	
	Dizziness (rare)		E	
	Headache (rare)		E	
	Sleep disorder (1%)		E	
Ophthalmic	Blurred vision (1%)		D	
Renal	Creatinine increased (rare)		E	
Reproductive and breast disorders	Androgen deprivation symptoms (up to 61%)		E	
Respiratory	Pneumonitis (rare)		E	
Urinary	Urine discoloration (amber / yellow-green)	I		

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse effects are androgen deprivation symptoms including **gynecomastia**, which is much less frequent when flutamide is used with an LHRH agonist. It is sometimes accompanied by **galactorrhea**. These effects usually disappear upon dose reduction or drug discontinuation.

Hepatotoxicity has been reported, usually in the first three months of treatment. Appropriate laboratory testing should be done regularly and at the first symptom/sign of liver impairment. Hepatic injury is usually reversible after discontinuation of therapy, but there have been reports of death following severe hepatic injury associated with flutamide.

The combined use of anti-androgen plus LHRH analogue / surgical castration increases **risk of cardiovascular disease and osteoporosis**. Androgen deprivation can adversely affect cardiovascular risk factors, such as increased body weight, reduced insulin sensitivity and/or dyslipidemia. Bone loss may occur during the hypoandrogenic state caused by long-term combined androgen blockade. Risk factors such as older patients, pre-existing osteopenia, family history of osteoporosis, chronic use of corticosteroids or anticonvulsants, or chronic alcohol/tobacco abuse should be carefully considered before starting treatment. **Reduction of glucose tolerance** has also been observed in patients receiving combined androgen blockade. Continuous androgen blockade has the potential to **increase QTc**, especially in patients with risk factors such as congenital long QT syndrome, abnormal electrolytes and concomitant medications which prolong QTc. **Anemia** is also a known physiologic effect of testosterone suppression.

Antiandrogen withdrawal syndrome has been reported. After discontinuation for disease progression, 6-8 weeks should elapse before making further treatment decisions.

back to top

E - Dosing

Refer to protocol by which patient is being treated. Flutamide should be used in combination with orchiectomy or with an LHRH agonist. Start simultaneously / 24 hours prior to LHRH agonist. If patient is receiving external beam radiation, start flutamide 8 weeks prior to radiation and continue throughout radiation treatment.

Adults:

Oral: 250 mg PO every 8 hours (TID)

Dosage with Toxicity:

Dosage in myelosuppression:

- No adjustment required

Dosage with Hepatic Impairment:

Discontinue flutamide if jaundice or liver transaminases ≥ 2-3 x ULN.

Dosage with Renal Impairment:

No adjustment required; slightly prolonged half-life in patients with CrCl < 29 mL/min. Not significantly removed by hemodialysis.

back to top

F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Swallow tablet whole with a glass of water; may be given with or without food.
- If a dose is missed, skip this and give the next dose as scheduled. Never double the dose to make up for the missed one.
- Avoid alcohol consumption as this may exacerbate flushing during flutamide treatment.

back to top

G - Special Precautions

Other:

Flutamide is **contraindicated** in patients who have moderate to severe hepatic impairment (LFTs ≥ 2-3 x ULN, increased bilirubin or jaundice), or who are hypersensitive to the drug or any component of its preparation. Flutamide is indicated only for use in male patients.

Use with caution in patients with cardiac disease since fluid retention may occur with the increase in testosterone and estradiol levels. Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Use with caution in patients with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease, or smokers, as exposure to the 4-nitro-3-fluoro-methylaniline metabolite may cause methemoglobinemia, hemolytic anemia, and cholestatic jaundice in these patients.

Although flutamide is not mutagenic, it is **fetotoxic, teratogenic** and may be **carcinogenic** and should not be used in women or during pregnancy. A few cases of breast cancer have been reported in male patients taking flutamide. Flutamide should not be used in breastfeeding since it suppresses lactation in animals and its secretion in breast milk is unknown. Increases in breast and testicular neoplasms have been seen in animal models. **Fertility** may be impaired.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Oral anticoagulant	↑ prothrombin time	Unknown	Monitor INR closely; may require anticoagulant dose adjustment
Theophylline	↑ theophylline concentration	Competition with flutamide for CYP1A2	Monitor
CYP 1A2, 3A4 inducers (strong)	↓ flutamide levels	May ↑ flutamide metabolism; Enzyme induction	Monitor
CYP1A2, 3A4 inhibitors (e.g. abiraterone)	↑ flutamide levels	May ↓ flutamide metabolism; Enzyme inhibition	Monitor; consider dose adjustment with strong inhibitors

Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Caution

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Blood glucose, HgA1c; in diabetic patients or patients at risk of hyperglycemia; regular
- Liver function tests; baseline, monthly for the first 4 months, then periodically and as clinically indicated
- ECG and electrolyte for patients at risk of QT prolongation
- Clinical evaluation for symptoms of hypogonadism, gynecomastia, osteoporosis, hyperglycemia, cardiovascular and GI effects
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR, in patients on anticoagulants; regular
- Methemoglobin concentrations in at risk patients (e.g. G6PD deficiency, hemoglobin M disease).

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

back to top

K - References

Aronoff GR, Berns JS, Brier ME, et al. Drug prescribing in renal failure: dosing guidelines for adults. 4th ed. Philadelphia (PA): American College of Physicians; 1999.

Flutamide: e-AHFS Drug Information. American Society of Health-Systems Pharmacists. Accessed Aug 15, 2013. Available from: http://www.ahfsdruginformation. com

Product Monograph: Euflex® (flutamide). Merck, October 15, 2012.

Flutamide: Merck Manual for Health Care Professionals. Available from: http://www.merckmanuals.com/professional/lexicomp/flutamide.html. Accessed July 15, 2014.

July 2014: Modified adverse effects, dosing, administration guidelines, special precautions, interactions and monitoring sections

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top