

DRUG NAME: Flutamide**SYNONYM(S):****COMMON TRADE NAME(S):** APO-FLUTAMIDE®, EUFLEX®, NOVO-FLUTAMIDE®**CLASSIFICATION:** hormonal agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Flutamide is a nonsteroidal antiandrogen which competitively inhibits the binding of androgens to the androgen receptor.¹ It is devoid of other endocrine activity. Flutamide is structurally and pharmacologically related to bicalutamide and nilutamide.²

Prostate cancer is primarily an androgen-dependent cancer and can be treated with surgical or medical castration. Luteinizing hormone releasing hormone agonists (LHRHa) suppress pituitary release of luteinizing hormone (LH) and result in medical castration. Unlike medical castration, nonsteroidal antiandrogens do not decrease the production of androgens. The initial stimulation of the pituitary caused by LHRHa produces an acute increase in the concentration of plasma testosterone accompanied by temporary worsening of symptoms (flare reaction). To avoid the flare reaction, antiandrogens should be given concurrently with the first administration of LHRHa.

Antiandrogens are also used in combination with LHRHa to inhibit the effects of testicular and adrenal androgens (maximum androgen blockade). In some patients with metastatic prostate cancer (15-20%),³ antiandrogen withdrawal may lead to a paradoxical decrease in serum prostate-specific antigen level (antiandrogen withdrawal syndrome).¹

PHARMACOKINETICS:

Oral Absorption	rapid and complete	
Distribution	steady-state achieved after the fourth dose	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	94-96%, 2-hydroxyflutamide: 92-94%
Metabolism	hepatic, rapid and extensive, involves the hepatic microsomal enzyme oxidation system ⁴	
	active metabolite ²	2-hydroxyflutamide
	inactive metabolite(s) ⁵⁻⁷	≥10 metabolites including 4-nitro-3-fluoro-methylaniline
Excretion	mainly renal ⁷	
	urine ⁸	primarily, <1% unchanged
	feces	4%
	terminal half life	4.7 h, 2-hydroxyflutamide: 6 h
	clearance	no information found
Elderly	terminal half life of 2-hydroxyflutamide: 8-9.6 h	

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:**

*Prostate cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindicated in patients with the following conditions¹:

- a history of hypersensitivity reaction to flutamide
- severe hepatic impairment or serum transaminase levels > 2 times the upper limit of normal

Caution:

Use flutamide with caution in patients with cardiac disease due to the potential for fluid retention secondary to elevated plasma testosterone and estradiol levels.¹

Special populations:

- Patients with **glucose-6-phosphate dehydrogenase deficiency**, **hemoglobin M disease**, and **smokers** are at risk of toxicities associated with 4-nitro-3-fluoro-methylaniline exposure, a metabolite of flutamide. These toxicities include methemoglobinemia, hemolytic anemia, and cholestatic jaundice. Methemoglobin concentrations should be periodically monitored in this population.^{2,5}
- Because of its intended use, safety and efficacy have not been established in **women** and **children**. Flutamide is indicated only for use in male patients.¹

Carcinogenicity: Flutamide is carcinogenic in rats at doses equivalent to ≥ 3 times the human dose.¹ No detailed information found in humans; although a causal relationship has not been established, malignant breast tumours have rarely been reported in men receiving flutamide.

Mutagenicity: Flutamide is not mutagenic in Ames test.¹ It is not known if flutamide is mutagenic in mammalian *in vitro* mutation test. It is not known if flutamide is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: A decrease in sperm count has been reported with flutamide use.¹ Because of its intended use, safety and efficacy have not been established in women.²

Pregnancy: FDA Pregnancy Category D.⁵ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk; because of its intended use, safety and efficacy have not been established in women.¹

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.⁹ When placebo-controlled trials are available, adverse events are included if the incidence is $\geq 5\%$ higher in the treatment group.

Side effects and incidences are those of flutamide when used with surgical or medical castration unless otherwise specified.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow/ febrile neutropenia	anemia (6%); hemolytic and macrocytic anemia, methemoglobinemia, and sulfhemoglobinemia have been reported
	leukopenia (3%), neutropenia (<1%)
	thrombocytopenia (1%)
cardiovascular (general)	hypertension (1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	myocardial infarction (<1%)
constitutional symptoms	fatigue
	increased appetite (4-6%), ^{6,7} weight gain ¹⁰
	insomnia (<1%)
dermatology/skin	photosensitivity reactions (<1%) ¹¹ ; including erythema, ulcerations, bullous eruptions, and epidermal necrolysis
	rash (3%), pruritis ¹² (<1%) ¹²
endocrine	gynecomastia (9%), monotherapy (34-42%) ⁶ ; reversible, breast tenderness (<1%); sometimes accompanied by reversible galactorrhea
	hot flashes (61%) ¹²
gastrointestinal	<i>emetogenic potential: rare</i> ¹³
	anorexia (4-6%) ⁷
	constipation
	diarrhea (12%, severe 5%); more likely than bicalutamide to cause severe diarrhea resulting in treatment discontinuation ¹²
	gastrointestinal disorders not otherwise specified (6%)
	indigestion (4-6%) ^{5,7}
	nausea and vomiting (11%)
hepatobiliary/pancreas	hepatic dysfunction including hepatic necrosis; see paragraph following the Side Effects table
lymphatics	edema (4%)
metabolic/laboratory	elevated serum transaminases; see paragraph following the Side Effects table
	elevated bilirubin
	elevated BUN; transient ⁶
	elevated gamma-glutamyl transferase
	elevated plasma testosterone and estradiol levels
	elevated serum creatinine; transient ⁶
musculoskeletal	weakness (<1%)
neurology	CNS reactions (1%); including drowsiness, dizziness, insomnia, confusion, depression, anxiety, and nervousness
ocular/visual	blurred vision (<1%)
pain	headache (<1%)
pulmonary	interstitial pneumonitis ⁵ (<1%) ^{5,14}
renal/genitourinary	change in urine colour to amber or yellow-green (<1%) ⁵
secondary malignancy	malignant breast neoplasms (<1%); causality not established
sexual/reproductive function	decreased sperm counts
	loss of libido, impotence ($\leq 100\%$) ⁹ ; decreased incidence with monotherapy ⁶
syndromes	lupus-like syndrome

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
vascular	pulmonary embolism (<1%)
	thrombophlebitis (<1%)

Adapted from standard reference¹ unless specified otherwise.

Hepatic dysfunction (<1%)^{5,12} including elevated serum transaminase levels, jaundice, hepatic encephalopathy, hepatic necrosis, and death have been reported with flutamide.¹ These toxicities typically occur within the first three months of treatment.¹ Appropriate liver function tests should be measured every three months.¹⁵ Liver function tests should also be obtained at the first signs and symptoms suggestive of liver dysfunction; e.g., nausea, vomiting, abdominal pain, lack of appetite, pruritis, fatigue, dark urine, persistent anorexia, unexplained “flu-like” symptoms, hyperbilirubinuria, jaundice, or right upper quadrant tenderness.^{1,11} If at any time a patient has jaundice, or transaminase levels rise > 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.¹

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
LHRH agonists ¹⁶	no documented influence on flutamide pharmacokinetics		
warfarin ^{1,16}	increased prothrombin time	unknown	monitor prothrombin time; adjust warfarin dose as required

Flutamide is a substrate of CYP 3A4 and CYP 1A2. Inducers and inhibitors of these enzymes may alter flutamide pharmacokinetics.¹⁷ Clinical significance is unknown.

SUPPLY AND STORAGE:

Tablets: Apotex supplies flutamide as a 250 mg film-coated scored tablet. Selected non-medicinal ingredients: lactose. Store at room temperature, protect from light and excessive moisture.¹

Novopharm supplies flutamide as a 250 mg tablet. Selected non-medicinal ingredients: lactose. Store at room temperature.¹¹

Schering Canada supplies flutamide as a 250 mg scored tablet. Selected non-medicinal ingredients: lactose. Store at room temperature, protect from light and excessive moisture.¹⁸

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy.

Adults:

Oral:	250 mg PO three times a day^{1,15,19} <ul style="list-style-type: none"> administer with food or on an empty stomach²; administering with food may help reduce nausea 	BCCA usual dose noted in <i>bold, italics</i>
Concurrent radiation:	no dose adjustment required ⁹	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required ^{2,20} ; half-life may be prolonged in patients with renal failure ¹²	
Dosage in hepatic failure:	not recommended in patients whose serum transaminase levels are >2 times the upper limit of normal ¹	
Dosage in dialysis:	not significantly removed by dialysis ^{8,12} ; supplemental dose not required ⁸	

Children:

no information found regarding the use of flutamide in pediatric oncology

REFERENCES:

1. Apotex Inc. APO-FLUTAMIDE® product monograph. Weston, Ontario; 28 October 2002.
2. McEvoy GK, editor. AHFS 2006 Drug Information®. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1056-1057.
3. Wirth MP, Hakenberg OW, Froehner M. Antiandrogens in the treatment of prostate cancer. *European Urology* 2007;51(2):306-314.
4. Juurlink D. Cytochrome P450 drug interactions, Compendium of Pharmaceutical Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2006. p. L53-59.
5. Rose BD editor. Flutamide. UpToDate 15.1 ed. Waltham, Massachusetts: UpToDate®; accessed 23 February 2007.
6. DRUGDEX® Evaluations (database on the Internet). Flutamide. Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 23 February 2007.
7. Solimando D.A. Jr. Cancer chemotherapy update: Updates of flutamide and nilutamide. *Hosp Pharm* 1997;32(5):635.
8. Anjum S, Swan SK, Lambrecht LJ, et al. Pharmacokinetics of flutamide in patients with renal insufficiency. *British Journal of Clinical Pharmacology* 1999;47(1):43-47.
9. Judy Sutherland MD. Personal communication. 11 June 2007; .
10. Spry NA, Kristjanson L, Hooton B, et al. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. *European Journal of Cancer* 2006;42(8):1083-1092.
11. Novopharm Limited. NOVO-FLUTAMIDE® product monograph. Toronto, Ontario; 4 September 2002.
12. USPDI® Drug Information for the Health Care Professional (database on the Internet). Antiandrogens, Nonsteroidal (Systemic). Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 23 February 2007.
13. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
14. MARTINDALE - The Complete Drug Reference (database on the Internet). Flutamide. Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 23 February 2007.
15. BC Cancer Agency Genitourinary Tumour Group. (GUPNSAA) BCCA Protocol Summary for Non-Steroidal Treatment of Prostate Cancer. Vancouver, British Columbia: BC Cancer Agency; 1 February 2007.
16. Drug Interaction Facts (database on the Internet). Flutamide. Facts and Comparisons 4.0, 2007. Available at: <http://online.factsandcomparisons.com>; Accessed 23 February 2007.
17. Lexi-Interact® (database on the Internet). Flutamide. Lexi-Comp Inc., Available at: <http://online.lexi.com>. Accessed 28 June 2011.
18. Schering Canada. EUFLEX® product monograph. Pointe Claire, Quebec; 21 February 2003.
19. BC Cancer Agency Genitourinary Tumour Group. (GUPLHRH) BCCA Protocol Summary for Therapy for Prostate Cancer Using LHRH Agonist (Goserelin, Leuprolide or Buserelin). Vancouver, British Columbia: BC Cancer Agency; 1 February 2007.
20. Aronoff GR, Berns JS, Brier ME, Golper TA, et al. Drug prescribing in renal failure: dosing guidelines for adults. 4th ed. Philadelphia (PA): American College of Physicians; 1999. p. 74.