DRUG NAME: Cabergoline

SYNONYM(S):

COMMON TRADE NAME(S): DOSTINEX®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cabergoline is a dopaminergic ergot derivative with longer lasting prolactin lowering activity than bromocriptine. Cabergoline may decrease hormone production and the size of prolactin-dependent pituitary adenomas[1] by inhibiting the release and synthesis of prolactin from the anterior pituitary gland.[2,3] The prolactin lowering effect is dose-related.[2]

PHARMACOKINETICS:

Oral Absorption	rapidly absorbed, unaffected by food	
Distribution	widely distributed,[4] time to peak 2-3 h, steady state achieved after 4 weeks	
	cross blood brain barrier?	yes
	volume of distribution	no information found
	plasma protein binding	40-42%
Metabolism	extensive hepatic metabolism, primarily via hydrolysis with minimal CYP450 mediated metabolism; undergoes first-pass metabolism	
	active metabolite(s)	no information found
	inactive metabolite(s)[4-6]	eight metabolites including 6-allyl-8b-carboxy-ergoline
Excretion	primarily hepatic[7]	
	urine[7]	18-22%, <4% unchanged after 20 days
	feces[7]	60-72% after 20 days
	terminal half life	63-69 h, hyperprolactinemic patients: 79-115 h
	clearance	no information found
Sex	no significant differences found[7]	
Elderly	no significant differences found[7]	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Pituitary tumours

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications[2]:

- a history of hypersensitivity reaction to ergot derivatives
- uncontrolled hypertension

Caution*[2]*:

- may cause hypotension; see paragraph following the **Side Effects** table
- hepatic impairment; see **Dosage Guidelines**
- with medications known to lower blood pressure; initial doses >1 mg may cause orthostatic hypotension; see paragraph following the **Side Effects** table
- history of, or current signs and/or clinical symptoms of respiratory or cardiac disorders linked to fibrotic tissue; see paragraph following the **Side Effects** table
- history of cardiovascular disease, Raynaud's syndrome, renal insufficiency, peptic ulcer, gastrointestinal bleeding
- history of serious, particularly psychotic, mental disease; particularly when patients are taking concomitant psychoactive medication
- when initiating therapy, the patient should not drive or engage in activities in which alertness is required

Carcinogenicity: Cabergoline is carcinogenic in mice and rats at doses equivalent to 4-7 times the maximum recommended human dose; due to species-specific differences in the role of prolactin, the relevance of these findings to humans is not known.[2]

Mutagenicity: not mutagenic in Ames test and mammalian *in vitro* mutation test.[2] Cabergoline is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: Cabergoline inhibits conception in rats at doses equivalent to 1/28 of the maximum recommended human dose. [2] Since cabergoline may restore fertility in hyperprolactinemic patients, women receiving cabergoline who would like to prevent pregnancy should use contraceptive measures.[8]

Pregnancy: FDA Pregnancy Category B.[9] Animal-reproduction studies have not shown a fetal risk but there are no controlled studies in pregnant women *or* animal-reproduction studies have shown a fetal risk (other than decreased fertility) not confirmed in controlled studies in pregnant women in the first trimester and there is no evidence of risk in later trimesters.

Breastfeeding is not recommended due to the potential secretion into breast milk.[2] Cabergoline may interfere with lactation due to its prolactin-lowering action; cabergoline should not be given to women who are breastfeeding or who are planning to breastfeed.[2]

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.[10] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** Side effects and incidence are those reported when cabergoline was used for cancer treatment.	
cardiovascular (arrhythmia)	palpitations (<1%)
cardiovascular (general)	***hypotension (1%), postural hypotension (4%)***; see paragraph following the **Side Effects** table
	valvulopathy; see paragraph following the **Side Effects** table
constitutional symptoms	fatigue (7-11%)
	hot flashes (1-3%)
gastrointestinal	*emetogenic potential: rare*[11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** Side effects and incidence are those reported when cabergoline was used for cancer treatment.	
	constipation (7-10%); more frequent during initiation of therapy, subsides after a few weeks[4]
	diarrhea (2%)
	dry mouth (2%)
	dyspepsia (2-5%)
	flatulence (2%)
	nausea (27-29%); dose-related, [4] more frequent during initiation of therapy, subsides after a few weeks,[4] less likely than bromocriptine to cause nausea[3]
	vomiting (2-4%)
neurology	anxiety (1%)
	depression (3%)
	dizziness (15-21%)
	impaired concentration (<1%)
	paresthesia (2%)
	somnolence (2-5%)
	syncope (1%)
pain	abdominal pain (5%); more frequent during initiation of therapy, subsides after a few weeks[4]
	breast pain (1-2%)
	headache (26%)
pulmonary	pulmonary fibrosis/pleural effusions; with long term use[4]; see paragraph following the **Side Effects** table
	rhinitis (<1%)

Adapted from standard reference[2] unless specified otherwise.

The major side effects of dopamine agonists are nausea, lightheadedness after standing, and somnolence.[1] These side effects are more likely to occur during treatment initiation or when the dose is increased.[1,3] Side effects may be minimized by starting with a low dose, increasing the dose slowly, using small doses more frequently, and taking the drug with food or at bedtime.[1,3]

The hypotensive effect of cabergoline is dose-dependent and typically occurs during initiation of therapy, or with a dose increase, within 6 hours of drug intake.[4,12] Initial doses >1 mg may cause orthostatic hypotension.[2] Use caution in patients taking concomitant medications known to affect blood pressure.[2] Monitor blood pressure periodically, especially during the first few days of therapy and with a dose increase.[4]

Fibrosis/Valvulopathy: As with other ergot derivatives, pleural effusion, pulmonary fibrosis, and valvular heart disease have been reported following long-term administration of cabergoline.[2] Some reports were in patients previously treated with other ergotinic dopamine agonists.[2] These effects may be dose-related[3]; use the lowest dose of cabergoline necessary to reduce prolactin levels to normal.[2,13] Use with caution in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. Changes may be reversible if cabergoline therapy is discontinued.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dopamine antagonists (e.g., phenothiazines, butyrophenones, thioxanthenes, metoclopramide, domperidone)[2]	reduced effect of cabergoline	antagonism of dopamine receptor stimulation	avoid concomitant use
macrolide antibiotics (e.g., azithromycin, clarithromycin, erythromycin)[2,14]	increased effect of cabergoline	increased bioavailability of cabergoline; suspected inhibition of P-glycoprotein and metabolism (CYP 3A4)	if used, monitor for cabergoline toxicity
other ergot alkaloids[2]	no documented interaction; theoretical risk of severe adverse effects (e.g., hypertension, MI)	additive toxicity	the manufacturer recommends avoiding concomitant use

SUPPLY AND STORAGE:

Oral: Squire Pharmaceuticals Inc supplies Pfizer-manufactured cabergoline as a scored 0.5 mg tablet. Selected non-medicinal ingredients: lactose. Store at room temperature.[15]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral[2]:

usual dose: ***0.5 mg PO twice a week***

- typical starting dose: 0.25 mg PO twice a week with food
- increase dose at monthly intervals by 0.5 mg a week until therapeutic response is achieved
- maximum weekly dose: 4.5 mg; higher doses have been used[16-18]
- total weekly dose may be given as a single dose or divided into two or more doses per week; doses $\geq$ 1 mg should not be given as a single weekly dose; initial doses >1 mg may cause orthostatic hypotension

Concurrent radiation: has been used[10]

Dosage in renal failure: cabergoline pharmacokinetics unaltered[2]; no specific guidelines found

Dosage in hepatic failure:

- mild-moderate hepatic impairment (Child-Pugh score <10): no change in C_{max} or AUC[2]
- severe hepatic impairment (Child-Pugh score >10): substantial increase in C_{max} and AUC[2]; decrease initial dose[7]

Dosage in dialysis: has been used

Children:

safety and efficacy have not been established in pediatric oncology[2]

REFERENCES:

1. Snyder PJ. Patient information: Lactotroph adenomas (prolactinomas). UpToDate 15.1, 26 October 2005. Available at: www.uptodate.com. Accessed 31 May 2007.
2. Pfizer Canada Inc. DOSTINEX® product monograph. Kirkland, Quebec; 14 September 2006.
3. Abrahamson MJ, Snyder PJ. Treatment of hyperprolactinemia due to lactotroph adenoma and other causes. UpToDate 15.1, 10 January 2007. Available at: www.uptodate.com. Accessed 31 May 2007.
4. DRUGDEX® Evaluations (database on the Internet). Cabergoline. Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 31 May 2007.
5. MARTINDALE - The Complete Drug Reference (database on the Internet). Cabergoline. Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 31 May 2007.
6. USPDI® Drug Information for the Health Care Professional (database on the Internet). Cabergoline (Systemic). Thompson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 31 May 2007.
7. Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. Clin Pharmacokinet 2003;42(7):633-645.
8. McEvoy GK, editor. AHFS 2007 Drug Information®. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 3674-3678.
9. Rose BD editor. Cabergoline. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 15.1; 2007.
10. Michelle Johnson MD. Personal communication. Endocrinologist, Vancouver, British Columbia; 27 September 2007.
11. 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.
12. Repchinsky C editor. DOSTINEX® monograph, Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2006. p. 710-712.
13. BC Cancer Agency Neuro-Oncology. (CNCAB) BCCA Protocol Summary for Second Line Suppressive Therapy for Prolactinomas using Cabergoline. Vancouver, British Columbia: BC Cancer Agency; 1 November 2002.
14. Drug Interaction Facts (database on the Internet). Cabergoline. Facts and Comparisons 4.0, 2007. Available at: http://online.factsandcomparisons.com. Accessed 31 May 2007.
15. Pfizer Canada Inc./ Squire Pharmaceuticals Inc. DOSTINEX® product monograph. Kirkland, Quebec; 15 April 2008.
16. Gillam MP, Middler S, Freed DJ, et al. The novel use of very high doses of cabergoline and a combination of testosterone and an aromatase inhibitor in the treatment of a giant prolactinoma. J.Clin.Endocrinol.Metab. 2002;87(10):4447-4451.
17. Shimon I, Benbassat C, Hadani M. Effectiveness of long-term cabergoline treatment for giant prolactinoma: Study of 12 men. European Journal of Endocrinology 2007;156(2):225-231.
18. Howell DL, Wasilewski K, Mazewski CM, et al. The use of high-dose daily cabergoline in an adolescent patient with macroprolactinoma. Journal of Pediatric Hematology/Oncology 2005;27(6):326-329.