DRUG NAME: Bromocriptine

SYNONYM(S):

COMMON TRADE NAME(S): APO-BROMOCRIPTINE®, PMS-BROMOCRIPTINE®

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Bromocriptine is a dopaminergic ergot derivative.[1] Bromocriptine may decrease hormone production and the size of prolactin-dependent pituitary adenomas[2,3] by inhibiting the release and synthesis of prolactin from the anterior pituitary gland.[1]

PHARMACOKINETICS:

Interpatient variability	variable GI absorption and first pass metabolism contributes to variability in plasma concentrations and dose response	
Oral Absorption	rapidly absorbed, 28-95%[4]	
Distribution	only 7% of the dose reaches systemic circulation unchanged due to first pass metabolism	
	cross blood brain barrier?[5]	yes
	volume of distribution	no information found
	plasma protein binding	96%
Metabolism	primarily hepatic, high hepatic extraction rate and first pass metabolism	
	active metabolite(s)	no information found
	inactive metabolite(s)[2]	lysergic acid and a peptide fragment
Excretion	primarily hepatic	
	urine[2]	3-6%
	feces[2,4,6]	95% via bile
	terminal half life	2-8 h; metabolites: 50-70 h
	clearance	no information found

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Pituitary tumours

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications[1,7]***:***
- history of hypersensitivity reaction to ergot derivatives
- uncontrolled hypertension

Caution:
- may cause hypotension[1]; see paragraph following the **Side Effects** table
- severe renal or hepatic impairment [1]; see **Dosage Guidelines**

- history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue[4]; see paragraph following the **Side Effects** table
- history of cardiovascular disease, Raynaud's syndrome, peptic ulcer, gastrointestinal bleeding
- history of serious, particularly psychotic, mental disease; particularly when taking concomitant psychoactive medication[1]
- episodes of sudden sleep onset have occurred, more commonly in patients with Parkinson's disease; the patient should use caution when driving or engaging in activities in which alertness is required[7]

Carcinogenicity: no information found

Mutagenicity: not mutagenic in Ames test and mammalian *in vitro* mutation test. Bromocriptine is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: Since bromocriptine may restore fertility in hyperprolactinemic patients, women receiving bromocriptine who would like to prevent pregnancy should use contraceptive measures.[2]

Pregnancy: FDA Pregnancy Category B.[4] Animal-reproduction studies have not shown a fetal risk but there are no controlled studies in pregnant women.[1]

Breastfeeding is not recommended due to secretion into breast milk.[4] Bromocriptine may interfere with lactation due to its prolactin-lowering action; bromocriptine should not be given to women who are breastfeeding or who are planning to breastfeed.[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.[8] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** Side effects and incidence are those reported when bromocriptine was used for cancer treatment.	
cardiovascular (arrhythmia)	palpitations[9] (2%)[9]
cardiovascular (general)	pericardial effusions and constrictive pericarditis (<1%); see paragraph following the **Side Effects** table
	hypotension (2-30%),[4,9] postural hypotension (1-10%)[4]; typically occurs during the first few days of treatment; see paragraph following the **Side Effects** table
constitutional symptoms	fatigue (8-14%)[9]; typically mild to moderate
gastrointestinal	*emetogenic potential: rare*[10]
	constipation (3-9%)[9]; typically mild to moderate
	diarrhea (3%); typically mild to moderate
	dry mouth (1%)[9]
	dyspepsia[9] (7%)[9]
	flatulence[9] (1%)[9]
	nausea (43-51%)[9]; typically mild to moderate

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** Side effects and incidence are those reported when bromocriptine was used for cancer treatment.	
	retroperitoneal fibrosis (<1%); with long-term use; see paragraph following the **Side Effects** table
	vomiting (5-7%)[9]; typically mild to moderate
neurology	anxiety[9] (1%)[9]
	depression[9] (2%)[9]
	dizziness (22-23%)[9]; typically mild to moderate
	impaired concentration[9] (<1%),[9] confusion and mental disturbances; including visual and auditory hallucinations, dose-related
	paresthesia[9] (3%)[9]
	somnolence (≤2%)[9]; including excessive daytime somnolence and episodes of sudden sleep onset[7] (<1%)[7]; more common in patients with Parkinson's disease[7]
	syncope (1%)[9]; typically occurs during the first few days of treatment
pain	abdominal pain/cramps (7-8%)[9]; typically mild to moderate
	headache (18-27%)[9]; typically mild to moderate; if severe, progressive, or unremitting, discontinue bromocriptine
pulmonary	pleural and pulmonary fibrosis/pleural effusions (<1%); with long term use; see paragraph following the **Side Effects** table
	rhinitis[9] (4%)[9]
syndromes	shock-like syndrome; secondary to postural hypotension
vascular	cold-induced vasospasm[2]

Adapted from standard reference[1] unless specified otherwise.

The major side effects of dopamine agonists are nausea, lightheadedness after standing, and somnolence.[3] These side effects are more likely to occur during treatment initiation or when the dose is increased.[2,3,11] Side effects are typically mild to moderate and 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.[2,3,11] If side effects are severe or persist, a dose reduction to 1.25 mg daily with gradual dose escalation may be considered.[1] In women, intravaginal administration may also decrease or prevent nausea[2,3,12]; see **Dosage Guidelines.**

The hypotensive effect of bromocriptine is due to its dopaminergic effect on vascular smooth muscle, peripheral sympathetic nerve terminals, and the CNS.[1] Monitor blood pressure periodically, especially during the first few days of therapy.[1] Use caution in patients taking concomitant medications known to affect blood pressure.[1] Hypotension occurs frequently but is symptomatic in only 1-5% of patients.[6]

Fibrosis(<1%)[1]: As with other ergot derivatives, pleural and pericardial effusion, pleural and pulmonary fibrosis, and retroperitoneal fibrosis have been reported following long-term administration of bromocriptine.[1] These effects may be dose-related[1]; use the lowest dose of bromocriptine necessary to reduce prolactin levels to normal.[12] Use with caution in patients with a history of, or current signs and/or symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. Changes may be reversible if bromocriptine therapy is discontinued.[1]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
alcohol[1,2]	alcohol intolerance and reduced tolerability to bromocriptine (<1%)[4]; especially with high doses of bromocriptine	unknown	caution
dopamine antagonists (e.g., phenothiazines, butyrophenones, thioxanthenes, metoclopramide, domperidone)[1,2]	reduced effect of bromocriptine	antagonism of dopamine receptor stimulation	avoid concomitant use
erythromycin[1] and other macrolide antibiotics[7]	increased effect of bromocriptine	may inhibit CYP3A4 metabolism of bromocriptine[4]	avoid concomitant use; if used, monitor for bromocriptine toxicity
grapefruit juice[13]	may increase plasma level of bromocriptine	may inhibit CYP3A4 metabolism of bromocriptine in the intestinal wall	regular monitoring; consider avoiding grapefruit and grapefruit juice for the duration of treatment
octreotide[7]	increased effect of bromocriptine	may increase plasma level of bromocriptine	if used, monitor for bromocriptine toxicity
other ergot alkaloids[2]	no documented interaction; theoretical risk of severe adverse effects (e.g., hypertension, MI)	additive toxicity	avoid concomitant use

Bromocriptine is a major CYP3A4 substrate; therefore, drugs or herbs that are CYP3A4 inhibitors may increase the serum levels/effects of bromocriptine.[4] Likewise, drugs or herbs that are CYP3A4 inducers may decrease the serum levels/effects of bromocriptine.[4]

SUPPLY AND STORAGE:

Oral: Apotex Canada Inc. supplies bromocriptine as a scored 2.5 mg tablet and 5 mg capsule. Selected non-medicinal ingredients: lactose. Store at room temperature and protect from light.[4]

Pharmascience Canada Inc. supplies bromocriptine as a scored 2.5 mg tablet and 5 mg capsule. Selected non-medicinal ingredients: lactose. Store at room temperature and protect from light.[14]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

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

Oral[1,8,12]:

usual dose: 5-7.5 mg PO daily, divided

- typical starting dose: 1.25 mg PO daily with food
- increase dose gradually every 2-7 days until therapeutic response is achieved[2,4]
- maximum daily dose: 20 mg; higher doses have been used[2,5]
- dose may be divided into two or more doses per day
- abrupt discontinuation has resulted in rare cases of a withdrawal reaction with symptoms similar to neuroleptic malignant syndrome[4]
- to minimize GI symptoms, oral tablets may be inserted vaginally for the first few doses; no first-pass effect with vaginal use, a dose reduction may be required[5,6]

Concurrent radiation:	has been used[8]
Dosage in renal failure:	safety and efficacy has not been established in patients with severe renal impairment[1]
Dosage in hepatic failure:	safety and efficacy has not been established in patients with severe hepatic impairment[1]; dosage reduction should be considered in patients with impaired hepatic function[2]; no specific guidelines found
Dosage in dialysis:	no information found

Children:

safety and efficacy have not been established in pediatric oncology[2,4]

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