DRUG NAME: Medroxyprogesterone

SYNONYM(S): MPA,[1] acetoxymethylprogesterone, methylacetoxyprogesterone,[2] 17-hydroxy-6-alpha-methylprogesterone[3]

COMMON TRADE NAME(S): PROVERA®

CLASSIFICATION: endocrine hormone

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

MECHANISM OF ACTION:

Medroxyprogesterone (MPA) is a progestin used in endometrial and breast cancers.[4] In endometrial cancer, MPA inhibits secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary gland. In breast cancer, MPA blocks the effect of adrenocorticotropic hormone (ACTH) from the pituitary gland.[5,6] Peripheral mechanisms of MPA include binding to progesterone, glucocorticoid, and androgen receptors[6-8] resulting in decreased number of estrogen receptors and decreased estrogen and progesterone levels peripherally in target tissues.[3,6] The growth inhibitory effects of progestins are not cell cycle phase-specific, but may be maximal in the G_1 phase.[9]

PHARMACOKINETICS:

Interpatient Variability	high doses are required to generate low-drug plasma levels and to overcome interpatient variation in absorption and metabolism[10,11]	
Oral Absorption	rapid; peak concentration in 2-4 h; up to 10% of dose absorbed[11]; bioavailability increased with food; steady state in 4-10 days[10,11]	
Distribution	widely distributed centrally and peripherally[2]	
	cross blood brain barrier?	yes
	volume of distribution[10]	25-300 L
	plasma protein binding	90%
Metabolism	primarily hepatic via CYP 3A4; more than 10 metabolites of unknown activity[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily via feces	
	urine	44% (as metabolites); primary metabolite: 6α-methyl-6β,17α,21-trihydroxy-4-pregnene-3,20-dione-17-acetate (8%)
	feces[10]	45-80% (as metabolites)
	terminal half life[4,7,10,11]	12-72 h
	clearance[10-12]	27-70 L/h
Elderly	no differences	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:
*endometrial cancer
*breast cancer

Other uses:
renal cell cancer[2]
uterine sarcoma[1,13]
ovarian cancer[3,13]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to medroxyprogesterone or progesterone[4]
- known or suspected pregnancy or women planning to become pregnant[4]

Carcinogenicity: Data is conflicting and clinical significance is unknown. In postmenopausal women, the use of combined estrogen plus progestin for hormone replacement therapy has been associated with an increased risk of invasive breast cancer.[2,4] Women younger than 35 years also appear to have an increased risk of breast cancer during the first four years of exposure to medroxyprogesterone. However, in contrast, in studies of medroxyprogesterone for contraception, overall breast cancer risk has been reported to be the same or slightly increased, with no evidence of increased overall risk of ovarian or cervical cancer. In other data, medroxyprogesterone appears to have a protective effect against endometrial cancer.[2] In animal studies, some species have developed malignancies; however, these models are no longer considered indicative of the hazard to women due to species differences in the sensitivity and metabolism of progestins.[4]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[4]

Fertility: Studies in humans have shown medroxyprogesterone suppresses testosterone production in the Lehdig cells of the testicles. NOTE: In the premenopausal woman, medroxyprogesterone given in appropriate therapeutic doses produces anovulation.[4]

Pregnancy: FDA Pregnancy Category X.[1,3] Studies in humans have demonstrated fetal abnormalities, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant. Avoid drugs that may interact with oral contraceptives. Minor birth defects have been reported in children whose mothers took progesterones during the first four months of pregnancy, including hypospadias in male infants and mild masculinization of the external genitalia in female infants.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk. Detectable amounts of progestin have been identified in breast milk; however, no adverse developmental or behavioural effects, even in puberty, have been reported in infants exposed to medroxyprogesterone through breast milk.[4]

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.[13,14] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group. **Side effects listed refer to oral medroxyprogesterone monotherapy data.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
endocrine	***Cushingoid symptoms***; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* rare[15]
	abdominal discomfort
	abdominal pain
	appetite, increased (66%)
	nausea
general disorders and administration site conditions	fatigue
	fever

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
immune system	anaphylaxis
investigations	***weight gain*** (36-97%)
investigations	cholestatic jaundice
metabolism and nutrition	folate, decreased
	glucose intolerance[13,16]
	hyperlipidemia[16]
nervous system	dizziness
	headache
	somnolence
psychiatric	depression
	insomnia
	nervousness[2]
reproductive system and breast disorders	***amenorrhea***
	breast tenderness
	irregular menstruation
	lactation disorder
	menorrhagia[2]
	vaginal discharge
skin and subcutaneous tissue	alopecia
	hirsutism
	pruritis
	rash acneiform
	urticaria
vascular	***cerebrovascular ischemia***; see paragraph following **Side Effects** table
	deep vein thrombosis[13]
	pulmonary embolism
	thrombophlebitis

Adapted from standard reference[4] unless specified otherwise.

Cushingoid symptoms may occur as a result of suppression of adrenocorticotropic hormone (ACTH). Symptoms may occur with high doses (e.g., 1000 mg/day)[5] and include "moon face", fluid retention, glucose intolerance, and elevated blood pressure. Clinical suppression of ACTH function has not been observed at low dose levels.[4]

Cerebrovascular ischemia may cause neurologic symptoms which include visual disturbances (diplopia, proptosis, or sudden partial or complete vision loss), migraine, transient aphasia, paralysis, or loss of consciousness.[4] If any of these symptoms occur, discontinue therapy with MPA until further evaluation.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aminoglutethimide[4,17]	50% reduction in serum medroxyprogesterone concentration; possible reduction in pharmacologic effect	possible increased hepatic metabolism of medroxyprogesterone	consider increasing medroxyprogesterone dose during concurrent administration of aminoglutethimide if an interaction is suspected
glucose tolerance test[4]	unreliable test results		discontinue medroxyprogesterone 2-4 weeks prior to test
plasma cortisol test[4]	unreliable test results		discontinue medroxyprogesterone 2-4 weeks prior to test
plasma estrogen test (in females)[4]	unreliable test results		discontinue medroxyprogesterone 2-4 weeks prior to test
plasma testosterone test (in males)[4]	unreliable test results		discontinue medroxyprogesterone 2-4 weeks prior to test
plasma progesterone test[4]	unreliable test results		discontinue medroxyprogesterone 2-4 weeks prior to test

Medroxyprogesterone is a **substrate** of CYP 3A4 isoenzyme. Strong inducers of CYP 3A4 may increase medroxyprogesterone metabolism, resulting in decreased plasma levels and therapeutic effect.[4,7,17] Strong inhibitors of CYP 3A4 may decrease medroxyprogesterone metabolism resulting in increased plasma levels and toxicity.

Medroxyprogesterone is a weak to moderate **inducer** of CYP 3A4 isoenzyme. Medroxyprogesterone may increase the metabolism of substrates of this enzyme and decrease their pharmacologic effect.[18]

SUPPLY AND STORAGE:

Oral: Apotex Inc. supplies medroxyprogesterone as 2.5 mg, 5 mg, 10 mg, and 100 mg scored tablets. Store at room temperature. Tablets contain lactose.[19]

Pfizer Canada Inc., Teva Canada Limited, and Dominion Pharmacal supply medroxyprogesterone as 2.5 mg, 5 mg, and 10 mg tablets. Store at room temperature. Tablets contain lactose.[4,20,21]

Pro Doc Ltée supplies medroxyprogesterone as 2.5 mg and 5 mg scored tablets. Store at room temperature. Tablets contain lactose.[22]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

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

Oral: ***200 mg*** (range 200-2400 mg) ***PO once daily***[4,23,24]
Administer with food or on an empty stomach. Doses greater than 200 mg may be given in divided doses.[4]

Dosage in renal failure: no information found

Dosage in hepatic failure: no information found

Dosage in dialysis: significant removal by dialysis is considered unlikely based on physicochemical properties of medroxyprogesterone[25]

Children: no information found

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