Drug Monograph

A - Drug Name

medroxyprogesterone

SYNONYM(S): methylacetoxyprogesterone; metipregnone; MPA

COMMON TRADE NAME(S): Provera® (Pfizer)

back to top

B - Mechanism of Action and Pharmacokinetics

Medroxyprogesterone is a long acting progestogen derived from soybeans. The mode of anticancer action of the progestins includes an indirect action on the hypothalamic-pituitary axis consisting of inhibition of gonadotrophin releasing hormone release as well as a direct action on estrogen receptors resulting in the inhibition of cellular proliferation. The growth inhibitory effects of progestins are not cell cycle phase-specific, but may be maximal in the G_1 phase of dividing cells.

Absorption	Bioavailability	oral: Rapid, subject to first-pass metabolism in the liver
	Peak plasma levels	Tmax: 2-4 hours (oral)
Distribution	Not elucidated, detectable in breast milk.	
	Cross blood brain barrier?	Yes
	Volume of distribution	No information found.
	PPB	90 %
Metabolism	Promptly metabolized in liver, first pass effect.	

	Active metabolites	No
	Inactive metabolites	Yes
Elimination	Urine (20-40%) and feces (5-13%)	
	Urine	20-42%
	Half-life	Apparent t ½ : 30 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Hormone dependent, recurrent metastatic breast cancer (in post-menopausal women)
- Recurrent and/or metastatic endometrial cancer
- Refer to the Product monograph for non-cancer indications

back to top

D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (1%)	E D
	Hypertension (less common)	E
	Tachycardia (rare)	E
	Venous thromboembolism (1%)	E D
Dermatological	Alopecia (rare)	E
	Hirsutism (1%)	D

	Other (chloasma)	D
	Rash (1%) (acne- rare)	E
Gastrointestinal	Abdominal pain (common)	E
	Bloating (common)	E
	Constipation	E
	Diarrhea (1%)	E
	Nausea, vomiting (4%)	I
	Weight changes (less common)	E
General	Fatigue (5%)	E
	Fluid retention (including effusions)	E
Hematological	Leukocytosis / thrombocytosis	E D
	Myelosuppression (rare)	E
	Sickle cell crisis (rare)	E
Hepatobiliary	Cholecystitis	D
	↑ LFTs	E
Hypersensitivity	Hypersensitivity (rare)	I
Infection	Infection (not related to myelosuppression; rare)	E
Injection site	Injection site reaction	I
Metabolic / Endocrine	Adrenal insufficiency (less common)	E
	Glucose intolerance	E
	Hyperlipidemia (abnormal lipids)	E
	Other corticosteroid effects	E D
Musculoskeletal	Musculoskeletal pain	E
	Osteoporosis (premenopausal)	D
Neoplastic	Secondary malignancy	D
Nervous System	Dizziness (6%)	E
	Headache (17%)	E
	Mood changes (2%)	E
	Neuropathy (1%)	E
	Somnolence / insomnia	E
Ophthalmic	Visual disorders (visual changes)	E
Reproductive and breast disorders	Estrogen deprivation symptoms (or androgen deprivation symptoms; less common)	E
	Gynecomastia / breast pain (less common)	E

	Vaginal bleeding	E
Respiratory	Dyspnea (1%)	E
Urinary	Urinary symptoms (less common)	E D

* "*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 side effects for medroxyprogesterone are abdominal pain, bloating, headache and anxiety.

Medroxyprogesterone can cause **mild fluid retention and body weight gain**, which is usually not clinically significant. The effect on body weight gain has been used therapeutically.

Medroxyprogesterone should be discontinued at the first sign of **thromboembolic disorders** or sudden onset of ocular problems (e.g., loss of vision, proptosis, and double vision). Patients with a history of migraine may be at increased risk of stroke.

May cause **acute hypercalcemia** in breast cancer patients with bone metastases during the first 2 weeks of therapy.

Exposure to medroxyprogesterone or other progestogens (in combination with estrogen) may increase the risk of **breast, ovarian and cervical cancer**, and is associated with an increased risk of stroke, myocardial infarction, dementia and thromboembolic disorders. The risk vs. benefit should be assessed before treatment.

Consider calcium and vitamin D supplementation in view of the risk of osteoporosis. For more information about bone health via dietary and lifestyle measures, see pamphlet, "Bone Health in Post Menopausal Women".

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Oral:

- Endometrial cancer: 200 to 400mg/day PO
- Breast Cancer: 400mg/day given in divided doses

Intramuscular injections:

- Renal and endometrial cancer: 400-1000mg / week intramuscularly (decrease to 400mg / month when stable)
- Breast cancer: 500mg/day intramuscularly for 28 days then 500mg intramuscularly twice per week

Dosage with Toxicity:

Toxicity	Dose
Myelosuppression	Continue treatment
Vaginal bleeding	Hold and investigate
Ophthalmic vascular disease	Discontinue
Arterial or vascular thromboembolism	Discontinue
↑ LFTs	Hold until ≤ ULN; discontinue if no recovery

Dosage with Hepatic Impairment:

Do not use in patients with abnormal LFTs.

Dosage with Renal Impairment:

No information found

Dosage in the elderly:

No adjustment required. There is an increased risk of arterial thromboembolism and breast cancer in patients ≥ 75 years.

Children:

No data available. There are no pediatric indications.

back to top

F - Administration Guidelines

- Oral self-administration; drug available by retail prescription.
- Depot formulation for intramuscular injections available.
- Medroxyprogesterone is not for i.v. use.

back to top

G - Special Precautions

Contraindications:

- patients with active or past history of significant arterial or venous thromboembolic disease, cerebrovascular disorders
- known or suspected pregnancy
- undiagnosed vaginal and/or urinary tract bleeding
- progestin dependent neoplasia, undiagnosed breast pathology
- liver dysfunction or disease
- preexisting ophthalmic vascular disease
- known hypersensitivity to medroxyprogesterone or any of its other ingredients

Other Warnings/Precautions:

- use with caution in patients with migraines,
- epilepsy,
- depression,
- severe cardiovascular disorders or diabetes,

- patients with galactose/lactose intolerance/malabsorption

Pregnancy and Lactation:

- Embryotoxicity: Yes
  May be carcinogenic. Medroxyprogesterone is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Documented in humans
  Breastfeeding is not recommended. Effects on the nursing infant is not significant but the long term effects of exposure on the infant are unknown.

back to top

H - Interactions

Medroxyprogesterone is metabolized primarily by CYP3A4. The clinical significance of drug interactions with CYP3A4 inhibitors and inducers has not been studied.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Amino-glutethimide	↓ medroxyprogesterone concentration and/or efficacy	Aminoglutethimide increases hepatic metabolism of medroxyprogesterone	Caution and monitor; clinical significance not known
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ medroxyprogesterone concentration and/or efficacy	↑ hepatic metabolism of medroxyprogesterone	Caution and monitor
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ medroxyprogesterone concentration and/or toxicity	↓ metabolism of medroxyprogesterone	Caution and monitor for toxicity
Thyroid function tests	↑ total T4 (thyroxine)	↑ thyroxine binding globulin	thyroid function unlikely to be affected

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Breast examination (including mammography and self-examination)	Baseline and routine
Pelvic examination (including Papanocolaou smear)	Baseline and routine
Complete physical examination	Baseline and routine

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version and monitor for thromboembolism, hot flashes, disease flare.

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Blood glucose in diabetes	Baseline and regular
Liver function tests	Baseline and regular
Cholesterol and triglycerides	Baseline and as indicated
Electrolytes (calcium)	Baseline and as indicated
Blood pressure	Baseline and as indicated

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

back to top

K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA).

Compendium of Pharmaceuticals and Specialities. Accessed 2007. Provera®. Canadian Pharmacists Association.

Compendium of Pharmaceuticals and Specialities. Accessed 2007. Depo-Provera®. Canadian Pharmacists Association.

Product Monograph: Provera ® (medroxyprogesterone acetate tablet). Pfizer Canada Inc, September 2014.

April 2015 updated adverse effects, special precautions and interactions 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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top