DRUG NAME: Megestrol

SYNONYM(S): megestrol acetate[1]

COMMON TRADE NAME(S): APO-MEGESTROL®, MEGACE®, MEGACE® OS, NU-MEGESTROL®, MEGACE® ES (USA)

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

A synthetic progestin with the same physiologic effects as progesterone.[1,2] Though its precise antineoplastic mechanism is unknown, megestrol is thought to act by suppressing release of luteinizing hormone from the pituitary gland or by a direct effect on cancer cells.[1-3] Megestrol has slight glucocorticoid activity and a very slight degree of mineralocorticoid activity.[2] Megestrol may also have antiandrogen activity, suppress adrenal androgens, and inhibit the enzyme 5 α–reductase.[1]

PHARMACOKINETICS:

Oral Absorption	variable, time to peak[1,2]: 1-5 h	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding[4]	high
Metabolism	inactivated in intestine and liver to free steroids and glucuronide conjugates	
	active metabolite(s)	no information found
	inactive metabolite(s)	yes
Excretion	respiratory excretion and fat storage may also occur	
	urine	66% (range: 57-78%)
	feces	20% (range: 8-30%)
	terminal half life	10-105 h; dose-dependent, 60-90 mg: 3.5 d, 160 mg: 38 h
	clearance	no information found

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Breast cancer
*Endometrial cancer

Other uses:
*Cancer cachexia
*Prostate cancer

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- history of thrombophlebitis[1]
- adrenocortical insufficiency[1]; see paragraph following the **Side Effects** table
- diabetes (due to risk of hyperglycemia)[5]

- should not be used as a diagnostic test for pregnancy[1]
- HIV infected women (due to risk of breakthrough bleeding)[1]
- should not be used prophylactically to avoid weight loss[5]

Carcinogenicity: An increased incidence of benign and malignant breast tumours has been reported in female dogs treated for up to seven years; an increased incidence has not been noted in monkeys when treated for up to ten years.[1] Dogs treated with 10-25 times the human dose, on a mg/kg basis, have developed mammary carcinoma with metastasis.[1] Pituitary tumours have occurred in female rats treated for 2 years.[1] Malignant lymphoma in mice may be stimulated.[1] The relevance of these findings to humans has not been established.[1]

Mutagenicity: studies not performed to date[1,2]

Fertility: In monkeys, megestrol caused decreased mean uterine weights and estrogen activity and a dose-related reduction in menses with near cessation of cyclic activity at 5 times the human dose on a mg/kg basis.[1] Impaired fertility in male offspring of female rats and dogs receiving doses equivalent to less than the recommended human dose has also been reported.[1,2] No information has been found regarding fertility in male animals.[2]

Pregnancy: FDA Pregnancy Category X.[3] Studies in animals or humans have shown fetal abnormalities,[1] or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Breastfeeding is not recommended due to the potential secretion into breast milk.[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.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** Side effects and incidence are those when used for cancer treatment, cancer cachexia information is not included. Megestrol is usually well tolerated.[2]	
auditory/hearing	hearing loss
cardiovascular (general)	***heart failure***; typically mild and resolves with initiation of diuretic therapy or adjustment of antihypertensive regimen[2]
	hypertension; typically occurs with high-doses (480-1600 mg),[2] typically mild and resolves with initiation of diuretic therapy or adjustment of antihypertensive regimen[2]
constitutional symptoms	fatigue[5]
	hot flashes
	weight gain (1-33%)[1,2]; associated with increased appetite, may be dose-related[2]
dermatology/skin	alopecia
	rash
endocrine	***adrenal insufficiency*** (<1%); see paragraph following **Side Effects** table
	cushingoid appearance
gastrointestinal	*emetogenic potential: rare*[7]
	nausea and vomiting (1-7%)[1,2,8]

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hemorrhage	vaginal bleeding (1-2%); including breakthrough and withdrawal[2,9] bleeding
lymphatics	edema (1-2%)
metabolic/laboratory	***hypercalcemia***; secondary to tumour flare, in patients with bone metastases[9]
	hyperglycemia; including new onset diabetes and exacerbation of preexisting diabetes[5]; secondary to pituitary adrenal axis abnormalities[5]
	laboratory evidence of pituitary-adrenal axis abnormalities
neurology	depression[8]
	mood changes/swings[9]
pulmonary	dyspnea (1-3%)[2]
sexual/reproductive function	gynecomastia[2]
	impotence[5]
syndromes	carpal tunnel syndrome
	Cushing's syndrome[5]
	tumour flare; with and without hypercalcemia
vascular	thrombosis/embolism; deaths have occurred

Adapted from standard reference[1] unless specified otherwise.

Adrenal insufficiency: Megestrol may rarely suppress the pituitary-adrenal axis during chronic administration.[1] Glucose intolerance, new onset diabetes, exacerbation of preexisting diabetes, and Cushing's syndrome have been reported.[5] Consider the possibility of adrenal insufficiency in patients being withdrawn from chronic therapy.[1] Symptoms may include fatigue, anorexia, hypotension, and asthenia.[10] Replacement therapy with a rapid-acting glucocorticoid should be considered.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
rifabutin[11]	no documented effect on megestrol pharmacokinetics		
zidovudine[11]	no documented effect on megestrol pharmacokinetics		

SUPPLY AND STORAGE:

Tablets: Apotex and Bristol-Myers Squibb supply megestrol as 40 mg and 160 mg scored tablets. Selected non-medicinal ingredients: lactose.[1,5] Store at room temperature.[1,5]

Additional information: Bristol-Myers Squibb supplies megestrol as a 240 ml bottle of 40 mg/mL suspension (only indicated for the treatment of anorexia in patients with a diagnosis of acquired immunodeficiency syndrome).[5]

MEGACE® ES 125 mg/mL (USA) is not equivalent on a mg per mg basis with other megestrol formulations due to its increased bioavailability[2,9] (625 mg MEGACE® ES is equivalent to 800 mg megestrol tablets or suspension).

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

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

160 mg or 125 mg/m^2 (range 160-1600 mg)[3] ***PO once daily***[1,2,12]
- dose may be divided into four doses a day

40-320 mg (range 40-800 mg) or 62.5 -250 mg/m^2 PO once daily[1,2,12]
- dose may be divided into four doses a day

400-800 mg (range 160-800 mg) PO once daily[1,2]
- for the treatment of cancer cachexia

Concurrent radiation: dosage adjustment not required[6]

Dosage in renal failure: no information found

Dosage in hepatic failure: no information found

Dosage in dialysis: it is not known if megestrol is removed by dialysis; due to low solubility it is unlikely to be removed by dialysis[1]

Children:

safety and effectiveness in children not established[1]; has been used[13]

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