



Progestins for Cachexia Therapeutic Class Review (TCR)

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FDA APPROVED INDICATIONS

Drug Name	Manufacturer	Indication
megestrol acetate (Megace®) oral suspension ¹	generic	Treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).
megestrol acetate (Megace ES®) oral suspension ²	PAR Pharmaceuticals	

*Megestrol acetate tablets are excluded from this review. The tablet formulation of megestrol acetate is only indicated for palliative treatment of advanced carcinoma of the breast or endometrium (recurrent, inoperable or metastatic disease).

OVERVIEW

Cachexia is a complex syndrome that includes weight loss, lipolysis, loss of muscle and visceral protein, anorexia, chronic nausea and weakness.³ Cachexia is usually defined as the loss of greater than 5% of an individual's baseline body weight over two to six months occurring with but not limited to a number of diseases, such as advanced cancer, chronic obstructive pulmonary disease (COPD), AIDS, Crohn's disease, and renal failure.⁴ Often cachexia and anorexia (lack of appetite) occur together. It is estimated that more than 80% of patients with advanced cancer or AIDS will develop cachexia before death.⁵

In addition to nutritional interventions, corticosteroids and progestational drugs are medications that have been used for the management of cachexia. For the purpose of this review, only the progestational drugs, megestrol acetate suspension (Megace) and megestrol acetate extra strength suspension (Megace ES) will be included. Both formulations of megestrol acetate suspension are solely indicated for the treatment of anorexia, cachexia or an unexplained, significant weight loss in patients with AIDS.

PHARMACOLOGY^{6,7}

Megestrol acetate is a synthetic derivative of progesterone. The exact mechanism of action as an appetite-enhancing agent in cachexia is unknown.

PHARMACOKINETICS^{8,9}

Megace ES uses NanoCrystal Dispersion® (NCD) technology that allows for a lower dosing regimen when compared to the original formulation.¹⁰ The usual daily dose of megestrol acetate suspension (40 mg/1 mL) is 800 mg, and megestrol acetate extra strength suspension (125 mg/1 mL) is 625 mg. The plasma concentrations of megestrol acetate after the administration of Megace ES 625 mg/5 mL suspension were equivalent to those after the administration of 800 mg/20 mL of Megace suspension under fed conditions. Therefore, Megace ES 625 mg/5 mL is considered bioequivalent to Megace 800 mg/20 mL suspension.¹¹

Peak plasma concentrations in cachectic males with AIDS were achieved in five hours following administration. The pharmacokinetics of the drug are linear in the dosing range used for the management of cachexia. The major route of elimination is in urine. The plasma elimination half-life ranges from approximately 13 to 104.9 hours (mean 34.2 hours).

CONTRAINDICATIONS/WARNINGS^{12,13}

Megestrol acetate oral suspension is contraindicated in patients with a history of hypersensitivity to the agent or any component of the formulation. It is also contraindicated in patients with known or suspected pregnancy.

Megestrol acetate oral suspension may cause fetal harm when administered to a pregnant woman.

The glucocorticoid activity of megestrol acetate is not fully understood. The possibility of adrenal insufficiency should be considered in any patient receiving or withdrawing from chronic therapy or who presents with signs and/or symptoms of hypoadrenalism in the stressed/non-stressed state.

Therapy for weight loss should only be instituted after treatable causes are sought and addressed. It is not intended for prophylactic use to avoid weight loss.

The use of megestrol acetate can exacerbate pre-existing diabetes, requiring increases of insulin doses. Chronic use of megestrol acetate has been associated with reported cases of new onset diabetes mellitus.

Furthermore post-marketing studies displayed limited reports of unsteady gait, shortness of breath and chest pain and gastrointestinal adverse effects have been observed in reported over dosage of megestrol acetate.

DRUG INTERACTIONS^{14,15}

Coadministration of megestrol acetate and indinavir (Crixivan[®]) may result in decreased levels of indinavir. Administration of a higher dose of indinavir should be considered when coadministered with megestrol acetate. Megestrol acetate at high doses may decrease the clearance of warfarin; therefore, clinicians should monitor INR levels while coadministering these two drugs.

ADVERSE EFFECTS^{16,17}

The most common adverse effects seen in clinical trials that were greater than those seen for placebo were impotence, rash, flatulence, insomnia, and hypertension.

Since the marketing of the drug there have been reports associated with megestrol acetate suspension of thromboembolic phenomena such as thrombophlebitis, deep vein thrombosis, and pulmonary embolism, as well as glucose intolerance. Breakthrough vaginal bleeding may occur in women due to progesterone agonistic effect.

SPECIAL POPULATIONS^{18,19,20}

Pediatric Use

Safety and effectiveness have not been established for pediatric patients for either concentration of megestrol acetate suspension.

Pregnancy

Both products are Pregnancy Category X.

Geriatric Use

Caution should be used in the geriatric population due to a greater potential for decreased hepatic, renal, or cardiac function. In clinical trials, an insufficient number of patients aged 65 years or older were included, and in general, dose selection should start at the lower range.

DOSAGES

Drug Name	Dosing	Availability
megestrol acetate (Megace)	800 mg/20 mL daily	Suspension: 40 mg/mL
megestrol acetate (Megace ES)	625 mg/5 mL daily	Suspension: 125 mg/mL

Megestrol acetate suspension is administered orally once daily. In clinical trials evaluating different dosing schedules, the two products were found to be equivalent.²¹

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no studies meeting the inclusion criteria.

SUMMARY

Cachexia is a debilitating and life-threatening syndrome characterized by anorexia, body weight loss, loss of adipose tissue and skeletal muscle. Both formulations of megestrol acetate suspension are clinically effective in increasing food intake resulting in weight gain. The original liquid formulation of megestrol acetate 800 mg/20 mL is bioequivalent to the extra strength liquid formulation of megestrol acetate 625 mg/5 mL.

REFERENCES

- 1 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 2 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 3 Bruera E. ABC of palliative care: anorexia, cachexia and nutrition. *BMJ*. 1997; 315:1219-1222.
- 4 Femia RA, Goyette RE. The science of megestrol acetate delivery: Potential to improve outcomes in cachexia. *BioDrugs*. 2005; 19(3):179-187.
- 5 Bruera E. ABC of palliative care: anorexia, cachexia and nutrition. *BMJ*. 1997; 315:1219-1222.
- 6 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 7 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 8 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 9 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 10 PAR. Megestrol acetate NCD oral suspension—PAR Pharmaceuticals: megestrol acetate nanocrystal dispersion oral suspension, PAR 100.2, PAR-100.2. *Drugs*. 2007; 8(4):251-4.
- 11 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 12 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 13 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 14 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 15 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 16 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 17 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 18 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.
- 19 Megace [package insert]. Princeton, NJ; Bristol-Myers-Squibb Company; April 2012.
- 20 Available at: www.clinicalpharmacology.com. Accessed April 2, 2014.
- 21 Megace ES [package insert]. Sun Valley, NY; PAR Pharmaceuticals; May 2013.