



1. PRODUCT NAME

APO-MEGESTROL 40mg & 160mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Megestrol acetate 40mg

Megestrol acetate 160mg

Excipient(s) with known effect

Contains lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APO-MEGESTROL 40mg: light blue, round, flat-faced, bevelled edge, scored tablets, engraved "APO" over "40" on one side, containing 40mg megestrol acetate

APO-MEGESTROL 160 mg: white, oval, biconvex, scored tablets, engraved "APO 160" on one side, containing 160mg megestrol acetate.

Please note: Not all strengths are marketed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-MEGESTROL is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e. recurrent, inoperable or metastatic diseases). It should not be used in lieu of currently accepted procedures such as surgery, radiation or chemotherapy.

APO-MEGESTROL is indicated for the treatment of anorexia, cachexia, or a significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

4.2 Dose and method of administration

Dose

Breast Cancer

160mg/day (160mg taken once daily).

At least two months of continuous treatment is considered an adequate period for determining the efficacy of megestrols

Best results are obtained in previously untreated receptor-positive cases that are more than five years post-menopausal (approximately 40% response rate). In patients with less favourable characteristics the response rate could be 15% or less.

Endometrial Carcinoma

40 – 320mg/day in divided doses (40 – 80mg one to four times daily or one to two 160mg tablets daily).

At least two months of continuous treatment is considered an adequate period for determining the efficacy of megestrol



APO-MEGESTROL

Cachexia

400 – 800mg/day

Use in Children

Safety and effectiveness in children have not been established.

Use in the elderly

Insufficient data from clinical studies of megestrol acetate are available for patients 65 years of age and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Megestrol acetate is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

Maximum Tolerated Daily Dose

Breast Cancer

160mg/day

Endometrial Carinoma:

320mg/day

Cachexia:

800mg/day

4.3 Contraindications

APO-MEGESTROL is contraindicated as a diagnostic test for pregnancy.

APO-MEGESTROL is contraindicated in patients with a history of hypersensitivity to megestrol acetate or any component of the formulation.

4.4 Special warnings and precautions for use

TUMOUROGENICITY

Administration of megestrol acetate in doses up to 0.25mg/kg/day for periods up to 7 years to female beagle dogs is associated with increased incidence of both benign and malignant tumours of the breast. Comparable studies in rats using doses of 10mg/kg/day for two years and in monkeys using doses up to 0.5mg/kg/day for 10 years have not been associated with any increased incidence of tumours. The relationship of the dog tumours to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing APO-MEGESTROL and in surveillance of patients on therapy.

In rats and beagle dogs, megestrol acetate increased blood glucose. In beagle dogs this was accompanied by changes in the eyes pancreas and kidneys that were indicative of diabetes mellitus. There are no specific precautions identified for the use of Megestrol acetate when used in humans as recommended. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer.

Use with caution in patients with a history of thrombophlebitis or diabetes mellitus.

The use of APO-MEGESTROL in other types of neoplastic disease is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetics Interactions

None known.

Pharmacodynamic Interactions

None known.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

The use of progestational agents during the first four months of pregnancy is not recommended (See below)

Animal studies have shown that high doses of progestagens can cause masculinisation of the female foetus.

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion or treat threatened abortion. There is no adequate evidence that such use is effective and there is evidence of potential harm to the foetus when such drugs are given during the first four months of pregnancy.

Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilised defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital heart defects and limb reduction defects. One study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted threatened abortion). Some of these exposures were very short and involved only a few days' treatment. The data suggest that the risk of limb reduction defects in exposed foetuses is somewhat less than 1 in 1,000.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female foetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female foetus, and because of the increased association of hypospadias in the male foetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminising effect on some male rat foetuses.

If the patient is exposed to megestrol acetate during the first four months of pregnancy, or if she becomes pregnant while taking this medicine, she should be apprised of the potential risks to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Breast-feeding

Very small amounts (approximately 0.1%) are excreted in mother's milk. It is however, not known whether these amounts exert any harmful effects on the newborn. Because of the potential for adverse effects on the newborn, nursing should be discontinued during treatment with APO-MEGESTROL

4.7 Effects on ability to drive and use machines

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

4.8 Undesirable effects

Weight Gain

Weight gain is a frequent side effect of megestrol acetate. This gain has been associated with increased appetite. Weight gain is caused by an increase in fat and body cell mass and is not necessarily associated with fluid retention.

Thromboembolic Phenomena

Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.

Other

Nausea, vomiting, edema and breakthrough uterine bleeding occur in approximately 1% to 2% of patients. Dyspnea, pain, Heart failure, hypertension, hot flushes, sweating, mood changes, cushingoid facies, tumor flare (with or without hypercalcemia), hyperglycemia, alopecia, carpal tunnel syndrome, asthenia, malaise, lethargy, rash, flatulence, diarrhoea and impotence have been reported.

Constipation and urinary frequency have been reported in patients who received high doses of megestrol acetate in clinical trials.

A rarely encountered side effect of prolonged administration of megestrol acetate is urticaria, presumably an idiosyncratic reaction to the drug.

APO-MEGESTROL is contraindicated as a diagnostic test for pregnancy.

Post-marketing Experience

The glucocorticoid activity of Megestrol acetate has not been fully evaluated. Clinical cases of glucose intolerance, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and overt Cushing's syndrome have been reported in association with the chronic use of Megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic Megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patients receiving or being withdrawn from chronic Megestrol acetate therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (e.g. hypotension, nausea, vomiting, dizziness or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognise inhibition of the hypothalamic-pituitary axis may result in death. Finally, in patients who are receiving or being with-drawn from chronic Megestrol acetate therapy, consideration should be given to the use of empiric therapy with stress doses of rapidly acting glucocorticoid in conditions of stress or serious intercurrent illness (e.g. surgery, infection)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

No serious side effects have resulted from studies involving megestrol acetate administered in dosages as high as 1600mg/day for 6 months or more. No acute toxicological effects have been recognised in

these studies. Oral administration of large single doses of megestrol acetate (5g/kg) did not produce toxic effects in mice.

Due to low solubility of megestrol acetate it is unlikely that dialysis would be an effective means of treating overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents / endocrine therapy / hormones and related agents / progestogens

ATC code: L02AB01

The chemical name of Megestrol acetate is 17 α -acetoxy-6-methylpregna-4,6-diene-3,20-dione.

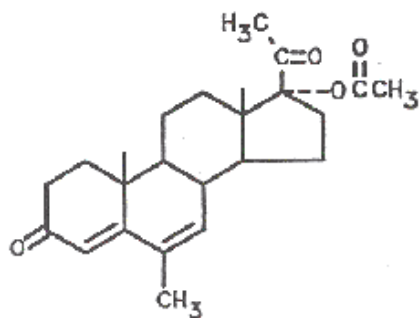
The empirical formula is $C_{24}H_{32}O_4$

The molecular weight is 384.5

Megestrol acetate is a white, crystalline solid and is chemically related to progesterone. It differs by the addition of a 17-acetoxy group, a double bond at position 6 and the presence of a methyl group.

Megestrol acetate is practically insoluble in water, soluble in alcohol (1 in 55), chloroform (1 in 8.0), ether (1 in 130), acetone and benzyl alcohol. Slightly soluble in fixed oils.

Chemical Structure



Mechanism of action

The precise mechanism by which megestrol acetate produces its antineoplastic effects against endometrial carcinoma is unknown, but an antiluteinizing effect mediated via the pituitary has been postulated. It is known to compete for progesterone, androgen and glucocorticoid receptors and effect pituitary functions. There is also evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. Likewise, the antineoplastic action for megestrol acetate on carcinoma of the breast is unclear.

Megestrol acetate has many of the properties of naturally occurring progesterone. Although its dose-dependent mode of action is identical to that of medroxyprogesterone acetate (MPA), its progestational potency is greater than MPA, with megestrol acetate 160 to 200mg p.o. equal to 1000 to 1500mg of MPA. The progestational potency of megestrol acetate is also greater than that of norethindrone and norethynodrel, but slightly less than that of chlormadinone acetate, and significantly less than that of norgestrel.

Megestrol acetate possesses significant antiestrogenic activity and has displayed antigonadotropic effects and slight but definite glucocorticoid activity. It has no estrogenic and little, if any, mineralocorticoid activity. In conventional doses it has not exhibited any anabolic or androgenic properties.

Megestrol acetate acts as an appetite enhancing agent in cachexia. The precise mechanism by which megestrol acetate produces its antianorexia and anticachexia effects is unknown at the present time.

The efficacy of megestrol acetate in anorexia and cachexia has been established in placebo-controlled trials where patients have received up to 800 mg/day of megestrol acetate. A dose response model was fitted to the maximum weight gain, which was shown to be statistically significant. The improvement in appetite was found to be statistically significant. Patients tolerated the drug well and no statistically significant differences were seen between treatment groups with regard to laboratory toxicities, new opportunistic infections, lymphocyte counts, T4 counts, T8 counts, or skin reactivity tests.

5.2 Pharmacokinetic properties

Absorption

In humans, megestrol acetate is rapidly absorbed following oral administration. Peak plasma levels are reached at about two hours, and the half-life is four hours. After a single oral administration of 60mg of megestrol acetate to healthy females, the plasma level reached a mean maximum of 43ng/ml after one to four hours; after 24 hours it was still detectable (9.6 to 29ng/ml) and after seven days it was in the range of 0.7 to 3.2ng/ml. There are several methods used to estimate megestrol acetate plasma levels, including mass fragmentography and radioimmunoassay. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotic administration, body weight, diet and liver function.

A clinical study in which megestrol acetate was administered in a 160mg single daily dose to metastatic breast cancer patients showed no major differences in responses to single daily dose megestrol acetate as compared to responses expected with a multiple daily dose regimen.

Distribution:

Similar peak plasma concentrations (90-110ng/mL) occur after the administration of one 160mg tablet or four 40mg tablets given over 24 hours. The extent of absorption (AUC) was also not different between the two dosage forms. The plasma half-life was 33 to 38 hours.

Metabolism:

The metabolic degradation of megestrol acetate was studied in five women; four received doses of 60 to 91mg and one received a dose of only 4mg. The compound was radioactively labelled on the 6-methyl group.

The biological half-life of the compound was three and a half days among the women who received the higher dose but was less than one day in the woman taking the lower dose. Three major metabolites, excreted as glucuronide conjugates, were identified.

The identification of these metabolites suggests the occurrence of hydroxylation at the C-2 position, the 6-methyl position, or both.

Other metabolites of megestrol acetate have been noted; although unconjugated steroids were quantitatively as significant as those excreted as glucuronides in the preceding study, their higher polarity and impurity prevented identification. The three identified metabolites accounted for only 5% to 8% of the administered dose.

Excretion:

The major route of elimination of megestrol acetate in humans is the urine. When radioactively labelled megestrol acetate was administered orally to humans in doses of four to 50mg, the urinary excretion within ten days ranged from 56.5% to 78.4% (mean 66.4%) and faecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). These values are in general agreement with those obtained with megestrol acetate in rabbits and with progesterone in humans.

Respiratory excretion as $^{14}\text{CO}_2$ and fat storage may have accounted for at least part of the radioactivity not found in the urine or faeces.

Clinical Implications of Pharmacokinetic Data

As megestrol acetate is primarily excreted in the urine and has a relatively long half-life, a potential for accumulation does exist. However, because megestrol acetate is relatively non-toxic, there are no recommendations at present for routine dosage-adjustment.

5.3 Preclinical safety data

Nil.

6. PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

The inactive ingredients for all APO-MEGESTROL tablets are: croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, lactose monohydrate and microcrystalline cellulose.

APO-MEGESTROL tablets contain lactose monohydrate.

APO-MEGESTROL tablets are gluten free

6.2 Incompatibilities

Nil.

6.3 Shelf life

40mg tablets 2 years from the date of manufacture.

160mg tablets 3 years from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25°C.

Protect from heat, light and moisture.

6.5 Nature and contents of container

APO-MEGESTROL 40mg: Bottles containing 100 tablets

APO-MEGESTROL 160mg: Bottles containing 30 or 100 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine



APO-MEGESTROL

8. SPONSOR

Apotex NZ Ltd.
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Telephone: (09) 444 2073
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9. DATE OF FIRST APPROVAL

11 July 2007

10. DATE OF REVISION OF THE TEXT

21 March 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.
8	Sponsor address updated, and email address added