

# New Zealand Data Sheet

## Megace

*Megestrol acetate 160mg tablets*

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### Presentation

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**Megace 160mg tablets** are off-white, oval, biconvex tablets with a bisect. Inactive ingredients are lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, silicon dioxide (colloidal) and povidone.

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### Uses

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#### **Actions**

##### Mechanism of Action

The anti-tumour action of megestrol acetate on carcinoma of the breast is unclear. However, it is known to compete for progesterone, androgen and glucocorticoid receptors and effect pituitary functions.

#### **Pharmacokinetics**

##### Absorption

Estimates of plasma levels of megestrol acetate are dependent on the measurement method used. Peak plasma concentrations occur 2 to 3 hours after a single oral dose 160mg tablets.

##### 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 metabolites are three glucuronide conjugates with hydroxylation occurring at either the 2-alpha, or the 6-methyl position or at both positions. Other metabolites occur but account for only 5 to 8% of the dose.

##### Excretion

Approximately 66% of an administered dose is excreted in the urine and approximately 20% in the faeces.

Respiratory excretion and fat storage may account for the fraction of an administered dose not found in urine or faeces.

### Clinical Implications of Pharmacokinetic Data

As megestrol acetate is primarily excreted in the urine and has a reasonably 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.

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## Indications

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

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## Dosage and Administration

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### Adult

#### Carcinoma of the breast

The recommended dose is 160 mg/day in single or divided doses. At least two months of continuous treatment is considered an adequate period for determining the efficacy of megestrol acetate.

Best results are obtained in previously untreated receptor-positive cases who 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.

The oral suspension should not be substituted for the tablets or vice versa.

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## Contraindications

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Allergy to megestrol acetate or any of the excipients. As a diagnostic test for pregnancy.

Women of child bearing potential should be advised to avoid becoming pregnant.

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## Warnings and Precautions

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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 uterine-relaxant properties of progesterone agents 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 to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for 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.

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

### **TUMOUROGENICITY**

Administration of megestrol acetate in doses up to 0.25mg/kg/day for periods up to seven years to female beagle dogs is associated with increased incidence of both benign and malignant tumours of the breast. Studies in rats using doses of 10 mg/kg/day for two years and in monkeys using doses up to

0.5 mg/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 megestrol acetate 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. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer.

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

### **USE IN PREGNANCY**

Pregnancy Category (Category D)

The use of progestational agents during the first four months of pregnancy is not recommended (see WARNINGS).

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

### **USE IN LACTATION**

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

### **RENAL IMPAIRMENT**

No information available.

### **HEPATIC IMPAIRMENT**

No information available.

### **PAEDIATRIC USE**

Safety and efficacy 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 difference 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.

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## **Adverse Effects**

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**Weight Gain:** Weight gain is a frequent side effect of MEGACE. This gain has been associated with increased appetite. Weight gain is caused by an increase in fat and body cell mass.

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

**Other Adverse Reactions:** Nausea, vomiting, edema, and breakthrough uterine bleeding occur in approximately 1% to 2% of patients. Dyspnea, pain, heart failure, hypertension, hot flashes, 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.

The glucocorticoid activity of MEGACE 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 MEGACE. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic MEGACE 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 MEGACE therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic MEGACE 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 a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognise inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic MEGACE 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)

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## Interactions

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No information is available regarding interactions with food, alcohol or other drugs.

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## Overdosage

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No serious side effects have resulted from studies involving MEGACE (megestrol acetate) administered in dosages as high as 1600mg/day. Oral administration of large single doses of megestrol acetate (5g/kg) did not produce toxic effects in mice.

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

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## Pharmaceutical Precautions

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Store below 30°C.

Shelf-life is 3 years.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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**Megace** is available as scored tablets containing **160mg megestrol acetate**, supplied in bottles of 30.

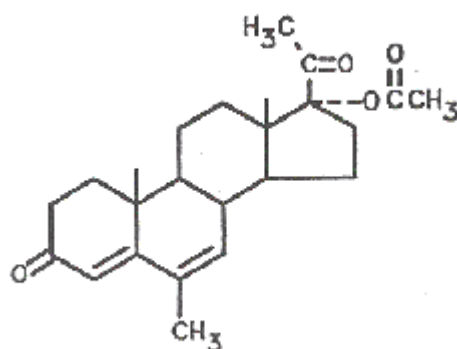
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## Further Information

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MEGACE (megestrol acetate). Megestrol acetate is a white, crystalline solid chemically described as 17 $\alpha$ -acetoxy-6-methylpregna-4,6-diene-3,20-dione. Megestrol acetate 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.

Structural formula:



Molecular weight: 384.5

Molecular formula: C<sub>24</sub>H<sub>32</sub>O<sub>4</sub>

MEGACE tablets contain 160 mg micronised megestrol acetate per tablet.

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## Date of Preparation

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14 July 2010