Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Megace Tablets 40 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Megestrol Acetate 40 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablets
White, flat faced, bevelled edge tablet with score and ‘40’on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Megace is a progestational agent, indicated for the treatment of certain hormone dependent neoplasms, such as endometrial or breast cancer.

4.2 Posology and method of adminstration

Breast cancer:

160 mg/day (40 mg qid or 160 mg taken once daily).

Endometrial cancer:

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

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

Children:

Megace is not recommended for use in children.

Elderly:

No dosage adjustment is necessary.

4.3 Contraindications

Megace is contra-indicated in patients who have demonstrated hypersensitivity to the drug or in patients with severe liver dysfunction or disease. Megace is also contra-indicated in patients with thromboembolic disorders.

4.4 Special warnings and precautions for use

Megace should be used with caution in patients with a history of thrombophlebitis.

This product should be used under the supervision of a specialist and the patients kept under regular surveillance.

This product can exert adrenocortical effects. This should be borne in mind in patient surveillance.

The use of this product in some patients may result in weight gain or fluid retention. This product should be used with caution in patients with impaired liver function.

Progesterone and certain progesterone's have been shown to produce reversible virilisation in some female offspring of women treated with such substances during pregnancy.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

None stated.

4.6 Pregnancy and lactation

Megace should not normally be administered to women who are pregnant or to mothers who are breast-feeding.

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

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 in male foetuses may be approximately doubled with the exposure to progestational drugs. There are insufficient data to quantify the risk to exposed female foetuses; however some of these drugs include mild virilisation of the external genitalia of the female foetuses.

If a patient is exposed to Megace during the first four months of pregnancy or if she becomes pregnant whilst taking Megace, she should be apprised of the potential risks to the foetus.

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

Because of the potential for adverse effects, nursing should be discontinued during treatment with Megace.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The major side-effect experienced by patients while taking megestrol acetate, particularly at high doses, is weight gain, which is usually not associated with water retention, but which is secondary to an increased appetite and food intake. Constipation and urinary frequency have been reported in patients who received high doses of megestrol acetate in clinical trials. Other occasionally noted side effects are nausea, vomiting, oedema and breakthrough uterine bleeding. Rare reports have been received of patients developing dyspnoea, pain, heart failure, hypertension, hot flushes, mood changes, cushingoid faces, tumour flare (with or without hypercalcaemia), hyperglycaemia, alopecia, carpal tunnel syndrome, diarrhoea and lethargy while taking megestrol acetate. Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported. A rarely encountered side effect

of prolonged administration of megestrol acetate is urticaria, presumably an idiosyncratic reaction to the drug. The drug is devoid of the myelosuppressive activity characteristic of many cytotoxic drugs and it causes no significant changes in haematology.

Pituitary adrenal axis abnormalities including glucose intolerance and Cushing's syndrome have been reported with the use of megestrol acetate. Clinically apparent adrenal insufficiency has been rarely reported in patients shortly after discontinuing megestrol acetate. The possibility of adrenal suppression should be considered in all patients taking or withdrawing from chronic megestrol acetate therapy. Replacement stress doses of glucocorticoids may be indicated.

4.9 Overdose

No serious side effects have resulted from studies involving Megace (megestrol acetate) administered in dosages as high as 1600 mg/day.

There is no specific antidote to overdosage and treatment should therefore be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Megace (megestrol acetate) possesses pharmacologic properties similar to those of natural progesterone. Its progestational activity is slightly greater than that of medroxyprogesterone acetate, norethindrone, norethindrone acetate and norethynodrel; slightly less than that of chlormadinone acetate; and substantially less than that of norgestrel.

Megestrol acetate is a potent progestogen that exerts significant anti-oestrogenic effects. It has no androgenic or oestrogenic properties. It has anti-gonadotropic, anti-uterotropic and anti-androgenic/anti-myotropic actions. It has a slight but significant glucocorticoid effect and a very slight mineralocorticoid effect.

The progestational activity of megestrol acetate has been assessed in a number of standard tests, including Clauberg - McPhail, McGinty, uterotropic and carbonic anhydrase tests in rabbits; pregnancy maintenance and delay-of-implantation tests in rats; endometrial response in rhesus monkeys; conversion of an oestrogen-primed endometrium to a secretory one in normal women and in those with secondary amenorrhea with resultant withdrawal bleeding; induction of pseudopregnancy for treatment of endometriosis; and the delay-of-menses and thermogenic tests. In all these tests, progestational activity was high.

It has been demonstrated that megestrol acetate blocks oestrogen effects in the uteri of rats and mice in human cervical mucus and vaginal mucosa. Anti-gonadotropic activity has been demonstrated in rats of both sexes.

5.2 Pharmacokinetic properties

Animal

Peak plasma levels occur four to six hours after oral administration of radioactively labelled megestrol acetate to female rats. High concentrations are found in the liver, fat, adrenal glands, ovaries and kidneys. Radioactivity is almost wholly cleared within a week, chiefly by biliary excretion to the faeces.

In dogs, megestrol acetate metabolites are excreted primarily in the faeces. In rabbits, the principal route of metabolic excretion is urinary and the major metabolites are the 2-alpha-hydroxy-6-hydroxymethyl and 6-hydroxymethyl derivatives.

Human

Peak plasma levels of tritiated megestrol acetate and metabolites occur one to three hours after oral administration. When 4 to 90mg of c-labelled megestrol acetate were administrated orally to women, the major route of drug

elimination was in the urine. The urinary and faecal recovery of total radioactivity within 10 days ranged from 56.6% to 78.4% (mean 66.4%) and 7.7% to 30.3% (mean 19.8%) respectively. The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). Megestrol acetate metabolites, which were identified in the urine as glucuronide conjugates, were 17-alpha-acetoxy-2-alpha hydroxyl-6-methylpregna-4, 6-diene-3, 20-dione; 17-alpha-acetoxy-6-hydroxmethylpregna-4, 6-diene-3, 20-dione; 17-alpha-acetoxy-2 alpha-hydroxy-6-hydromethylpregna-4, 6-diene-3, 20-dione; these identified metabolites accounted for only 5-8% of the administrated dose.

Serum concentrations were measured after the administration of single and multiple oral doses of megestrol acetate. Both men and women participated in the study. All were healthy volunteer adults not more than 65 years of age and the women were postmenopausal.

Megestrol acetate is readily absorbed following oral administration of 20, 40, 80 and 200 mg doses. Megestrol serum concentrations increase with increasing doses, the relationship between increasing dosage and increasing serum levels not being arithmetically proportional. Average peak serum concentrations for the four doses tested were 89, 190, 209 and 465 ng/ml.

Mean peak serum concentrations are found three hours after single-dose administration for all dosage levels studied. The serum concentration curve appears biphasic, and the beta-phase half-life is 15 to 20 hours longer.

After multiple doses over a three-day period, serum levels increase each day and are estimated to reach 80% to 90% predicted steady-state levels on the third day.

5.3 Preclinical safety data

No further relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia spray dried
Calcium phosphate dibasic
Lactose
Magnesium stearate
Maize starch
Silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years - Blister packs *(Marketed Pack)*
5 years - Amber glass bottles.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles with white or black plastic closure and foil/pump lubricated liner or ‘click-lok’ closure system, containing 100 tablets.
PVC/aluminium blister packs of 100 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Holdings Limited
t/a Bristol-Myers Pharmaceuticals
Swords
County Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 48/27/1

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Date of last renewal: 01 December 2002

10 DATE OF REVISION OF THE TEXT

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