SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MEGACE 160 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:

Megestrol acetate	160 mg

Excipients:

Lactose monohydrate	224.50 mg
Sodium starch glycolate	28 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet
It is in the form of white to off-white, oval, biconvex tablets with “160” engraved on one side and a scoring line on the other side, with no visible contamination.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
MEGACE is indicated for the palliative treatment of advanced breast cancer (e.g., recurrent, inoperable or metastatic cases) and for the treatment of cancer-related anorexia or weight loss.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
In each of the following indications, continuous treatment for at least two months is recommended.

Breast cancer: 160 mg/day (single or divided doses)
Anorexia or weight loss: 400 – 800 mg, once daily.

Method of administration:
MEGACE tablet is taken with a sufficient amount of water (e.g. a glass).

Additional information for special populations
Renal/Hepatic impairment:
No dose adjustment is required in patients with renal impairment. 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.
No dose adjustment is required in patients with hepatic impairment.

Pediatric population:
Safety and efficacy has not been studied in pediatric patients.
MEGACE is not recommended for use in children.

Geriatric population:
Data from clinical studies of megestrol acetate are not sufficient to determine whether response in patients over 65 years of age differs from younger patients. Caution should be exercised when

MEGACE is used in elderly patients.

Due to decreased hepatic, renal and cardiac functions and other medications used for another disease, care is taken to keep the initial dose low and the frequency of use higher.

4.3 Contraindications
Contraindicated in patients with hypersensitivity to megestrol acetate or any of the excipients listed in section 6.1.
MEGACE is contraindicated during pregnancy.

4.4 Special warnings and precautions for use
Precautions:
MEGACE should be used with caution in patients with a history of thrombophlebitis and in patients with severe hepatic dysfunction.

This product should be used under specialist supervision and the patient should be monitored regularly. This product may exhibit adrenocortical effects. For this reason, patient monitoring should be considered.

There are insufficient data from clinical studies of megestrol acetate to determine whether patients aged 65 years and over respond differently to the drug than younger patients. Other reported clinical experience has not identified a difference in drug response between elderly and younger patients. In general, caution should be exercised when used in elderly patients, considering the degree of decreased liver, kidney or heart function and concomitant diseases or other drug treatments. 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. Since renal function deceleration may be more common in elderly patients, caution should be exercised during treatment with megestrol acetate and monitoring of the patient's renal function may be useful.

Since it contains lactose, patients with rare hereditary problems of glucose-galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

MEGACE 160 mg tablet contains sodium. This medicinal product contains 28 mg sodium starch glycolate in each tablet. This should be taken into account in patients on restricted sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction
Interaction studies have not been conducted.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy Category: X

Women of childbearing potential/Birth control (Contraception):
Megestrol acetate has harmful pharmacological effects on pregnancy and/or the fetus/newborn.
Women of childbearing potential should avoid becoming pregnant while using this medication. They should use effective birth control during treatment.

Pregnancy:
The use of MEGACE is not recommended during pregnancy.

There are several reports that in utero exposure to progestational drugs during the first trimester of pregnancy is associated with genital abnormalities in male and female fetuses. The risk of hypospadias, which occurs in 5 to 8 of every 1,000 male births in the general population, may be doubled with these medications. There are insufficient data to determine the risk to female fetuses, but some of these drugs cause mild virilization of the external genitalia of female fetuses.

If a patient takes MEGACE during the first four months of pregnancy or becomes pregnant while taking this drug, the patient should be informed of the potential risks to the fetus.

Breast-feeding:
The use of MEGACE is not recommended during breastfeeding.
Breastfeeding should be discontinued during treatment with MEGACE due to potential side effects.

Reproductive ability / Fertility:
Fertility and reproduction studies with high doses of megestrol acetate have shown signs of reversible feminization in some male rat fetuses.

4.7 Effects on ability to drive and use machines
Megestrol acetate has no known effect on the ability to drive and use machines.

4.8 Undesirable effects
The main side effect observed in patients taking megestrol acetate, especially in high doses, is weight gain, which is usually not associated with fluid retention but is followed by increased appetite and food consumption. Weight gain is associated with increased fat and cell mass in the body.

Constipation and frequent urination have also been reported in patients receiving high doses of megestrol acetate in clinical studies.

Urticaria, a possible idiosyncratic reaction to the drug, is an uncommon side effect of long-term use of megestrol acetate. This drug lacks the myelosuppressive activity typical of many cytotoxic drugs and does not cause significant changes in hematology, biochemistry, or urinalysis.

With the use of megestrol acetate, glucose intolerance, new-onset diabetes, exacerbation of preexisting diabetes with decreased glucose tolerance, abnormalities of the pituitary-adrenal axis, including Cushing's syndrome, have been noted. Clinically significant adrenal insufficiency has been reported rarely shortly after discontinuation of megestrol acetate. The possibility of adrenal suppression should be considered in all patients receiving or discontinuing chronic megestrol acetate therapy. Replacement therapy with glucocorticoids may be required.

Clinical Experience:
Adverse reactions reported during clinical experience were listed by system organ class and using MedDRA terms, and the following frequency groups were used for listing:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (cannot be estimated from available data)

Benign and malignant neoplasms (including cysts and polyps)
Common: Tumor flare [#]

Endocrine disorders
Very common: Adrenal insufficiency, cushingoid, Cushing's syndrome

Metabolism and nutrition disorders
Very common: Diabetes mellitus, glucose intolerance, hyperglycemia, increased appetite

Psychiatric disorders
Common: Mood changes

Nervous system disorders
Common: Carpal tunnel syndrome, lethargy

Cardiac disorders
Common: Cardiac failure

Vascular disorders
Very common: Thrombophlebitis, pulmonary embolism* , hypertension, hot flushes

Respiratory, thoracic and mediastinal disorders
Very common: Dyspnea

Gastrointestinal disorders
Very common: Constipation
Common: Nausea, vomiting, diarrhea, bloating

Skin and subcutaneous tissue disorders
Common: Rash, alopecia

Renal and urinary disorders
Common: Pollakiuria

Reproductive system and breast disorders
Common: Menorrhagia, erectile dysfunction

General disorders and administration site conditions
Common: Asthenia, pain, edema.

Investigations
Very common: Weight increase

With or without hypercalcemia
* Pulmonary embolism (fatal in some cases)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
Studies using megestrol acetate doses of 1600 mg/day for 6 months or longer have not shown any acute toxic effects.

Overdose cases have also been reported post-marketing. In overdose, diarrhea, nausea, abdominal pain, shortness of breath, cough, unsteady gait, weakness, and chest pain have been observed. There is no specific antidote to this medicine. In the event of overdose, appropriate supportive treatment should be applied.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Progesterones
ATC code: L02AB01

MEGACE (megestrol acetate) has similar pharmacological properties to natural progesterones. Its progestational activity is slightly higher than that of medroxyprogesterone acetate, norethindrone, norethindrone acetate, and norethynodrel; slightly less than that of chlormadinone acetate; and much less than that of norgestrel.

Megestrol acetate is a potent progestogen with significant anti-estrogenic effects. It has no androgenic or estrogenic properties. It has anti-gonadotropic, anti-uterotropic and anti-androgenic/anti-myotropic effects. Megestrol acetate has a mild but significant glucocorticoid effect and little mineralocorticoid effect.

5.2 Pharmacokinetic properties
General properties
Absorption:
Megestrol acetate is rapidly absorbed after oral administration at doses of 20, 40, 80 and 200 mg. Megestrol serum concentrations increase with increasing doses. The relationship between increasing dose and serum level is not arithmetically proportional. Mean peak serum concentrations for the 4 doses tested were 89, 190, 209, and 465 ng/mL.

Distribution:
Mean peak plasma concentrations were found 3 hours after a single dose administration for all doses studied. The serum concentration curve appears biphasic, with a beta-phase half-life of 15 to 20 hours.

After multiple dosing over a 3-day period, serum levels increase each day and are estimated to reach 80% to 90% of the predicted steady-state level by day 3.

Biotransformation
The metabolites of megestrol acetate, 17-alpha-acetoxy-2-alpha-hydroxy-6-methylpregna-4,6-diene-3,20-dione; 17-alpha-acetoxy-6-hydroxymethyl pregna-4,6-diene-3,20-dione and 17-alpha-acetoxy-2-alpha-hydroxy-6-hydroxymethylpregna-4,6-diene-3,20-dione, were found in urine as glucuronide conjugates. These metabolites accounted for only 5 to 8% of the administered dose.

Serum concentrations were measured after single and multiple oral doses of megestrol acetate. Adult male and postmenopausal female volunteers no older than 65 years of age were included in the study.

Elimination
Peak plasma levels of tritium-labeled megestrol acetate and its metabolites are reached within 1 to 3 hours after oral administration. When 4 to 91 mg of c-labeled megestrol acetate were administered orally to women, drug elimination was primarily via the urine. Urinary and fecal 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. Total radioactivity recovered was between 83.1% and 94.7% (average 86.2%).

5.3 Preclinical safety data
Administration of megestrol acetate to female dogs up to 7 years of age has been associated with an increased incidence of benign and malignant mammary tumors. In comparable studies in rats and monkeys, there was no increase in tumor incidence. The relationship between the increase in tumors in dogs due to megestrol acetate and the possible risk in humans is unknown, but when prescribing megestrol acetate, the benefit-risk ratio should be taken into account and the patient should be monitored during treatment.

Fertility and reproduction studies involving high doses of megestrol acetate have shown transient feminizing effects in some male rat fetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Microcrystalline cellulose
Colloidal silicon dioxide
Povidone K30
Sodium starch glycolate
Magnesium stearate
Purified water*
*Used during manufacturing. It is not contained in the finished product tablet.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of container
In blister packages of 30 tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal products or waste materials should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER
231/50

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization: 04.05.2011
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT