SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TARLUSAL 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Medroxyprogesterone acetate 5 mg

Excipient(s) with known effect:
Lactose monohydrate 82.38 mg
Sucrose 1.47 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
White, odorless, round tablets, flat on both sides, debossed with the letter "T" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TARLUSAL tablets are indicated for
- Functional metrorrhagia (hyperestrinism, and caused by hyperestrinism),
- Secondary amenorrhea (hyperestrinism, and caused by hyperestrinism; given together with estrogens in the latter case),
- Endometriosis.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
In gynecology,
Use of combined estrogen/progestin therapy in post-menopausal women should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated (see section 4.4).

During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual differences (see Section 4.4).

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in a woman without an intact uterus.

Endometriosis
For the treatment of endometriosis, TARLUSAL is taken 10 mg three times a day for 90 consecutive days, beginning on the first day of the menstrual cycle.

Secondary amenorrhea:
For the treatment of secondary amenorrhea, 2.5 to 10 mg daily for 5 to 10 days for 3 consecutive cycles. Estrogen should be used concomitantly with TARLUSAL treatment in patients with endometrial hypotrophy.

Functional metrorrhagia
In gynecological disorders related to irregular menstruation, TARLUSAL is administered for 8-10 days in the second half of menstruation. In severe metrorrhagia, the dose can be increased up to 15-25 mg per day.

Method of administration
It is taken orally. The tablets should be swallowed whole, without chewing or crushing, with some water (e.g., a glass of water).

Additional information on special populations
Renal impairment
The effect of renal disorders on the pharmacokinetics of medroxyprogesterone acetate has not been evaluated in any clinical study. However, since almost all of medroxyprogesterone acetate is known to be eliminated by hepatic metabolism, no dose adjustment is necessary in women with renal impairment.

Hepatic impairment
The effect of hepatic disorders on the pharmacokinetics of medroxyprogesterone acetate has not been evaluated in any clinical study. However, it is known that almost all of medroxyprogesterone acetate is eliminated by hepatic metabolism, and steroid hormones are poorly metabolized in patients with severe hepatic impairment.

Pediatric population
Not applicable as it is not used in this population.

Geriatric population
There is no indication for use in this age group.

4.3 Contraindications

TARLUSAL is contraindicated in
- Patients with known hypersensitivity to medroxyprogesterone or any of the excipients,
- Vaginal bleeding of unknown cause,
- Thrombophlebitis, thromboembolic events,
- Cerebral apoplexy,
- Severe liver dysfunction,
- Known or suspected pregnancies,
- Known or suspected malignancies in the breast.

4.4 Special warning and precautions for use

- Unexpected vaginal bleeding during therapy with medroxyprogesterone acetate should be investigated. It should not be given until a definitive diagnosis is made.

- Medroxyprogesterone acetate may cause some degree of fluid retention; therefore, caution should be exercised in the treatment of all patients with a pre-existing medical condition (epilepsy, migraine, asthma, cardiac or renal dysfunction) who may be adversely affected by fluid retention.

- Patients with a history of depression treatment should be carefully monitored during the use of medroxyprogesterone acetate. Some patients may complain of premenstrual-like depression during treatment.

- Appropriate contraceptive methods should be recommended, as doses up to 30 mg per day may not suppress ovulation.

- Decreased glucose tolerance may be observed in some patients using medroxyprogesterone acetate. Diabetic patients should be carefully observed during this treatment.

- In endometrial or endocervical tissue examination, the pathologist (laboratory) should be informed that the patient is using medroxyprogesterone acetate.

- The physician/laboratory should be informed that the use of medroxyprogesterone acetate may decrease levels of the following hormone levels
  a) Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
  b) Plasma/urinary gonadotrophins (e.g., LH and FSH)
  c) Sex hormone binding globulin.

- Medication should not be re-administered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be re-administered.

- Medroxyprogesterone acetate has not been causally associated with the induction of thrombotic or thromboembolic disorders; however, the use of medroxyprogesterone acetate is not recommended in patients with a history of venous thromboembolism (VTE). Discontinuation of the drug is recommended in patients who develop VTE during treatment with medroxyprogesterone acetate. Rare cases of thrombo-embolism have been reported, especially at high doses.

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

TARLUSAL contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

TARLUSAL may affect plasma aminoacid, serum alkaline phosphatase, urinary nitrogen, hepatic function tests, coagulation tests, metyrapone test, pregnanediol determination, and thyroid function tests.

Rare interactions with oral anticoagulants have been reported.

Aminoglutethimide administered concomitantly with high-dose oral medroxyprogesterone acetate can significantly lower serum concentrations of medroxyprogesterone acetate. Users of high-dose oral medroxyprogesterone acetate should be warned of the possibility of reduced efficacy with the use of aminoglutethimide.

Additional information on special populations:
There are no interaction studies in special populations.

Pediatric population:
There are no interaction studies in pediatric populations.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy Category: X

Women of childbearing potential/Contraception
Women of childbearing potential must use effective contraception during treatment.
If the patient becomes pregnant while using this medicine, she should be warned of the potential risk to the fetus.

Pregnancy
TARLUSAL is suspected to cause serious birth defects if administered during pregnancy.
TARLUSAL is contraindicated during pregnancy (see section 4.3).
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.
A negative pregnancy test is required before treatment begins.

Lactation
Medroxyprogesterone acetate and its metabolites are excreted in breast milk. There is no evidence to suggest that this poses any risk to the breastfed infant (see section 5.2).
TARLUSAL should not be used during breastfeeding.

Reproductive ability/Fertility
Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

4.7 Effects on ability to drive and use machines

No adverse effects have been reported.

4.8 Undesirable effects

The following terms and frequencies are used:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The frequencies of undesirable effects given below by system organ class are infrequently associated with the use of progesterone.

Immune system disorders
Rare: Hypersensitivity reactions (e.g. anaphylaxis and anaphylactoid reaction, angioedema)

Endocrine disorders
Not known: Prolonged anovulation

Metabolism and nutritional disorders
Rare: Edema/fluid retention, weight change

Psychiatric disorders
Rare: Depression, insomnia, nervousness

Nervous system disorders
Rare: Dizziness, headache, somnolence

Vascular disorders
Rare: Thromboembolic events
Not known: Thrombophlebitis, cerebral thrombosis and embolism

Respiratory, thoracic and mediastinal disorders
Not known: Pulmonary embolism

Gastrointestinal disorders
Rare: Nausea

Hepatobiliary disorders
Not known: Cholestatic icterus/jaundice

Skin and subcutaneous tissue disorders
Rare: Acne, alopecia, hirsutism, pruritus, rash, urticaria

Reproductive system and breast disorders
Rare: Galactorrhea, breast tenderness, breast pain

General disorders and administration site conditions
Rare: Fatigue

Investigations
Rare: Decreased glucose tolerance
Not known: Changes in cervical secretions

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Overdose treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens

ATC code: G03DA02

Medroxyprogesterone acetate (17a-hydroxy-6a-methylprogesterone acetate) is a progesterone derivative.

Mechanism of action:
Medroxyprogesterone acetate is a synthetic progestin (structurally similar to the endogenous progesterone hormone) that has been shown to have several pharmacological effects in the endocrine system, including:

- Inhibition of pituitary gonadotropins (FSH and LH);
- Decreased ACTH and hydrocortisone blood levels;
- Decrease in circulating testosterone;
- Decrease in circulating estrogen levels (resulting in an increase in testosterone clearance as a result of FSH inhibition and enzymatic induction of hepatic reductase and thus a decrease in the conversion of androgen to estrogen).

All of these effects cause some pharmacological effects described below:

Gynecology
Medroxyprogesterone acetate converts the proliferative endometrium to the secretory endometrium when administered orally or parenterally at recommended doses to women with adequate endogenous estrogen. This drug is considered to lack significant estrogenic activity, although androgenic and anabolic effects have been observed. Depo-medroxyprogesterone acetate, when administered parenterally, inhibits gonadotropin production and prevents follicular maturation and ovulation. Available data indicate that this does not occur when the generally recommended oral dose is taken as a single daily dose.

5.2. Pharmacokinetic properties

General properties
Absorption
Oral medroxyprogesterone acetate is rapidly absorbed, reaching maximum concentration in 2 to 4 hours. The half-life of oral medroxyprogesterone acetate is approximately 17 hours.

Taking medroxyprogesterone acetate with food increases its bioavailability. When a 10 mg oral dose of medroxyprogesterone acetate was taken immediately before or after a meal, the mean C_{max} (51% and 77%, respectively) and AUC of medroxyprogesterone acetate (18% and 33%, respectively) increased. The half-life of medroxyprogesterone acetate is not changed with food.

Distribution
Medroxyprogesterone acetate is approximately 90% protein bound, primarily to albumin; no medroxyprogesterone acetate binding occurs with sex hormone binding globulin. Unbound medroxyprogesterone acetate modulates pharmacological responses.

Biotransformation
Following oral dosing, medroxyprogesterone acetate is extensively metabolized in the liver by A-ring and/or side-chain hydroxylation, followed by conjugation and elimination in the urine. At least 16 medroxyprogesterone acetate metabolites have been identified. Results from a study designed to measure medroxyprogesterone acetate metabolism suggest that the cytochrome P450 3A4 isoenzyme in human liver microsomes is responsible for medroxyprogesterone acetate metabolism.

Elimination
Medroxyprogesterone acetate metabolites are excreted in the urine mainly as glucuronide and a small amount as sulfate conjugates. After a 10 mg or 100 mg dose in patients with fatty liver, the mean dose excreted as intact medroxyprogesterone acetate in the 24-hour urine is 7.3% and 6.4%, respectively. The elimination half-life of oral medroxyprogesterone acetate is 12 to 17 hours.

Linearity/Non-linearity
Plasma concentration is generally linear with given dose; however, significant individual variation can be observed.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility
Long-term intramuscular administration of depot medroxyprogesterone acetate has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of medroxyprogesterone acetate to rats and mice.

Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Talc
Maize starch
Sucrose
Calcium stearate
Mineral oil (liquid paraffin)

6.2 Incompatibilities

It does not have any known incompatibilities

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at room temperature below 25°C and in a dry place. Protect from light.

6.5 Nature and contents of container

Blisters of 12 tablets covered with transparent foil on one side and aluminum foil on the other side. Each cardboard box contains 12 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed according to local disposal

regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece/ISTANBUL - TURKEY

8. MARKETING AUTHORIZATION NUMBER

145/87

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 08.08.1988
Date of last renewal :

10. DATE OF REVISION OF THE TEXT