# DANILON®
(Dydrogesterone)

## 1. NAME OF THE PRODUCT
***DANILON***® (Dydrogesterone) 10mg Tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
***DANILON***® **10mg Tablet**
Each film coated tablet contains:
Dydrogesterone……...10mg

## 3. PHARMACEUTICAL FORM
Film coated tablet.

**Appearance:** White to off-white, biconvex coated tablet, plain from one side and break line on the other side.

## 4. CLINICAL PARTICULARS
### 4.1. THERAPEUTIC INDICATIONS:
- Symptomatic relief of mild to moderate vasomotor symptoms associated with menopause.
- Prevention of postmenopausal osteoporosis, if other treatments are unsuitable.

**Progesterone deficiencies:**
- Treatment of dysmenorrhoea.
- Treatment of endometriosis.
- Treatment of secondary amenorrhoea.
- Treatment of irregular cycles.
- Treatment of dysfunction uterine bleeding
- Treatment of threatened miscarriage
- Treatment of habitual miscarriage
- Treatment of infertility due to luteal insufficiency.
- Luteal support as part of an Assisted Reproductive Technology (ART) treatment

### 4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
**Posology:**
The dosage, regimen and duration of treatment should be adjusted according to the severity of the symptoms and the clinical response.

**Progesterone insufficiencies:** Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response. Symptomatic relief of mild to moderate vasomotor symptoms associated with menopause; prevention of postmenopausal osteoporosis;

- Continuous sequential therapy: An oestrogen is dosed continuously and one tablet of 10mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner.
- Cyclic therapy: When an oestrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10mg dydrogesterone is added for the last 12 – 14 days of oestrogen therapy.

If ultrasound or endometrial biopsies would reveal inadequate progestational response, 20mg dydrogesterone should be prescribed.
**Dysmenorrhoea:** 10mg twice daily from day 5 to day 25 of the menstrual cycle.
**Endometriosis:** 10mg two or three times daily from day 5 to day 25 of the cycle or continuously.
**Dysfunctional bleeding (to arrest bleeding):** 10mg twice daily for five to seven days. **DANILON®** should be given with oestrogen.
**Dysfunctional bleeding (to prevent bleeding):** 10mg twice daily from day 11 to day 25 of the cycle. **DANILON®** should be given with oestrogen.
**Amenorrhoea:** An oestrogen once daily from day 1 to day 25 of the cycle, together with 10mg dydrogesterone twice daily from day 11 to day 25 of the cycle.
**Irregular cycles:** 10mg twice daily from day 11 to day 25 of the cycle.
**Threatened miscarriage:** 40mg at once, then 10mg every eight hours until symptoms remit.
**Habitual miscarriage:** 10mg twice daily until the twentieth week of pregnancy.
**Infertility due to luteal insufficiency:** 10mg daily from day 14 to day 25 of the cycle. The treatment should be continued for at least 6 consecutive cycles. It is advisable to continue this treatment during the first months of any pregnancy using the doses stated with respect to habitual miscarriage.
**Luteal support as part of an Assisted Reproductive Technology (ART) treatment:** 10mg three times daily (30mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed.
There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents aged 12 to 18 years has not been established.

**Method of Administration:**
For oral use.
For administration of higher dosages, the tablets should be taken evenly distributed over the day.

When taking 1 film-coated tablet daily, it is recommended to always take the daily dose at the same time of day, e.g. always in the morning or always in the evening. When taking 2 film-coated tablets daily, it is recommended to take one in the morning and one in the evening.

## 4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Known or suspected progestogen-dependent tumours (e.g. meningioma).
- Unexplained vaginal bleeding.
- Contraindications for the use of estrogens should be taken into account when used in combination with dydrogesterone.
- Severe acute and chronic liver diseases as well as disorders in the metabolism of bile pigments (e.g. Dubin-Johnson syndrome, Rotor syndrome).
- Previous or existing liver tumours.
- Thrombophlebitis and thromboembolic diseases.
- Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion/miscarriage.

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

If dydrogesterone is prescribed for the treatment of irregular bleeding, the etiology of this bleeding should be clarified.

Breakthrough bleeding and spotting may occur during the first months of treatment. If such bleeding occurs later in the course of the treatment or after the end of the treatment, the cause should be investigated and under some circumstances an endometrial biopsy should be performed to exclude endometrial malignancy.

If any of the following disorders occurs for the first time or worsens during use, discontinuation of the treatment must be considered:

- Exceptionally severe headache, migraine or symptoms which might suggest cerebral ischaemia
- A notable rise in blood pressure
- Occurrence of venous thromboembolism

In cases of habitual and threatened miscarriage, the viability of the foetus should be determined and checked during treatment to see if the pregnancy is continuing and whether the embryo is still alive.

**Conditions which need monitoring:** It is known that the following rare conditions can be influenced by sex hormones, and during pregnancy or during the use of sex hormones may occur or worsen: cholestatic jaundice, herpes gestationis, severe pruritus, otosclerosis and porphyria. Patients with a history

of depression should be monitored carefully. If severe depression recurs, the treatment with dydrogesterone must be stopped.

**Other conditions:** Patient with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

**In higher doses, caution is advised with:** Cerebral apoplexy (also in the medical history).

**The following warnings and precautions apply when using dydrogesterone in combination with estrogens in hormone replacement therapy (HRT):** HRT should only be initiated for treatment of those postmenopausal symptoms that adversely affect quality of life. In each individual case, a careful appraisal of the risks and benefits should be undertaken at least annually. HRT should only be continued as long as the benefit outweighs the risk. There are limited data for the assessment of the risks associated with HRT in the treatment of premature menopause. Due to the low level of absolute risk in younger women, the balance of benefits and risks for these women may be more favorable than in older women.

**Medical examinations/follow-up:** Before initiating or re-instituting hormone replacement therapy (HRT), a complete medical history (including family history) should be taken. Physical (including gynaecological and mammary) examinations should be guided by the history and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature suited to each individual woman. Women should be advised what changes in their breasts should be reported to their doctor (see 'Breast cancer' below). Investigations, including imaging procedures, e.g., mammography, should be carried out in accordance with the applicable screening guidelines, taking into account the medical situation of the individual woman.

**Endometrial hyperplasia and carcinoma:** In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased with long- term use of oestrogens without the addition of progestogen. Depending on the duration and the oestrogen dose, the risk is 2 to 12 times higher than in women who do not take any oestrogen. After stopping the oestrogen treatment, the risk remains for at least 10 years. This additional risk can be prevented by combining the oestrogen therapy for at least 12 days per month/28-day cycle with a progestogen, such as dydrogesterone. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting occur after taking the therapy for some time or if they continue after the treatment has ended, further investigation is then indicated. This may mean that an endometrial biopsy should be carried out so as to be able to rule out malignancy.

**Breast cancer:** There is evidence of an increased risk of breast cancer in women receiving combined HRT with estrogen and progestogen or HRT containing estrogen alone, the risk depends on the duration of HRT.

**Ovarian cancer:** Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies including the WHI study, suggest that the use of combined HRTs may be associated with a similar, or slightly smaller, risk.

**Venous thromboembolism:** HRT is associated with a 1.3-3-fold risk of venous thromboembolism (VTE), especially of deep vein thrombosis or pulmonary embolism. The occurrence of such an event is much more likely in the first year of HRT use than later. Patients with known thrombophilia have an increased risk of VTE. HRT may add to this risk and is therefore contraindicated in these patients. Generally recognized risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobility, obesity (BMI > 30kg/$m^2$), pregnancy/postpartum, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobility is to occur after elective surgery, it is recommended to temporarily discontinue HRT 4 to 6 weeks before this surgery. Treatment should not be resumed until the woman is fully mobile again. In women who do not have a personal history of VTE but have a first-degree relative who suffered thrombosis at a young age, screening for thrombophilia may be considered. Before, the patient should be carefully instructed of the limitations of this procedure (screening will only identify a part of the defects leading to thrombophilic disorders). If a thrombophilic defect is found and if in addition thrombosis in family members are known or if it is a 'severe' defect (e.g., antithrombin, protein S and/or protein C deficiency or a combination of defects), HRT is contraindicated. In women who are already chronically treated with anticoagulants, the benefit/risk ratio should be carefully weighed before HRT use. If VTE develops after initiation of HRT, the drug must be discontinued. Patients shall be advised to contact their physician as soon as they are aware of the onset of any potential symptom of thromboembolism (especially painful swelling of a leg, sudden chest pain, dyspnoea).

**Coronary artery disease:** There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. Combined oestrogen-progestogen therapy: The relative risk of CAD during use of combined oestrogen- progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of

extra cases of CAD due to oestrogen-progestogen use is very low in women close to menopause, but will rise with more advanced age.

**Ischemic stroke:** Treatment with an estrogen-progestogen combination and estrogen alone is associated with up to a 1.5-fold increase in the risk of ischemic stroke. The relative risk is independent of age and the time elapsed since menopause. But since the baseline risk of stroke is highly depending on age, the overall risk of stroke in women under HRT will increase with age.

**Reasons for immediate discontinuation of therapy:** Therapy is to be discontinued immediately if there is a contraindication and if one of the following situations occurs:

- migraine-like or unusually severe headache
- acute vision impairment

**Excipient:** This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

The major metabolic pathway generating the main pharmacologically active metabolite 20α dihydrodydrogesterone (DHD) is catalyzed by aldo-keto reductase 1C (AKR 1C) in human cytosol. Next to the cytosolic metabolism there are metabolic transformations by cytochrome P450 isoenzymes (CYPs), nearly exclusively via CYP3A4, resulting in several minor metabolites. The main active metabolite DHD is substrate for metabolic transformation by CYP3A4.

Therefore, the metabolism of dydrogesterone and DHD may be increased by concomitant use of substances known to induce these CYP enzymes such as anticonvulsants (e.g. Phenobarbital, phenytoin, carbamazepine), anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and herbal preparations containing e.g. St John's Wort (*Hypericum perforatum*), sage, or gingko biloba. Ritonavir and nelfinavir, although known as strong cytochrome enzyme inhibitors, by contrast exhibit enzyme-inducing properties when used concomitantly with steroid hormones.

Clinically, increased metabolism of dydrogesterone may lead to a decreased effect and changes in the bleeding pattern.

Dydrogesterone and DHD do not inhibit or induce CYP drug- metabolizing enzymes at clinically relevant concentrations.

## 4.6. FERTILITY, PREGNANCY AND LACTATION:

**Fertility:** There is no evidence that dydrogesterone decreases fertility at therapeutic doses.

**Pregnancy:** It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect

of dydrogesterone use during pregnancy. Some progestogens have been reported in literature to be associated with an increased risk of hypospdias. However, due to confounding factors during pregnancy, no definitive conclusion can be drawn regarding the contribution of progestogens to hypospadias. Clinical studies, where a limited number of women were treated with dydrogesterone early in pregnancy, have not shown any increase in risk. No other epidemiological data are hitherto available. Effects in non-clinical embryo-fetal and post-natal development studies were in line with the pharmacological profile. Untoward effects occurred only at exposures which exceeded the maximum human exposure considerably, indicating little relevance to clinical use. Dydrogesterone can be used during pregnancy if clearly indicated.

**Breast-feeding:** There are no data on the excretion of dydrogesterone in mother's milk. Experience with other progestogens indicates that progestogens and their metabolites pass into breast milk in small amounts. It is not known whether there is any risk to the baby. Therefore, Dydrogesterone 10mg should not be taken while breast-feeding.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Dydrogesterone 10mg has a minor effect on the ability to drive and use machines. Dydrogesterone may rarely cause mild somnolence and/or dizziness, especially during the first hours after use. Therefore, machines and vehicles should only be operated with caution.

## 4.8. UNDESIRABLE EFFECTS:

During treatment with dydrogesterone, symptoms may occur that are also common in the early phase of pregnancy, such as loss of appetite, stomach pressure, nausea, oedema and weight gain, nervous restlessness, dizziness, worsening of mood and calf cramps. These complaints disappear when the treatment is stopped.

The most commonly reported adverse reactions in patients treated with dydrogesterone in clinical trials on indications without estrogen use are migraine/headache, nausea, menstrual disorders and breast pain/tension.

The adverse reactions ranked using the following convention: 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); not known (cannot be estimated from the available data).

**Neoplasms benign, malignant and unspecified (incl. cysts and polyps):**

***Rare:*** Increase in size of progestogen dependent tumours (e.g. meningioma)

**Blood and lymphatic system disorders:**

***Rare:*** Haemolytic anaemia

**Psychiatric disorders:**

***Uncommon:*** Depressed mood

**Immune system disorders:**
***Rare:*** Hypersensitivity reactions
**Nervous system disorders:**
***Common:*** Headache, migraine
***Uncommon:*** Dizziness
***Rare:*** Somnolence
**Gastrointestinal disorders:**
***Common:*** Nausea, vomiting, abdominal pain
**Hepatobiliary disorders:**
***Uncommon:*** Hepatic function abnormal (with asthenia or malaise, jaundice and abdominal pain)
**Skin and subcutaneous tissue disorders:**
***Uncommon:*** Dermatitis allergic (e.g. rash, urticaria, pruritus)
***Rare:*** Angioedema
**Reproductive system and breast disorders:**
***Common:*** Menstrual disorders (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation), breast pain/tenderness
***Rare:*** Breast swelling
**General disorders and administration site conditions:**
***Rare:*** Oedema
**Investigations:**
***Uncommon:*** Weight gain

### 4.9. OVERDOSE:

**Symptoms:** Dydrogesterone is a drug of very low toxicity. Nausea, vomiting, somnolence and dizziness are symptoms that theoretically may occur in the event of an overdose. There are no known cases where an overdose of dydrogesterone has resulted in harmful consequences.

**Treatment:** There are no specific antidotes and treatment should be symptomatic.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES:

**Pharmacotherapeutic group:** Sex hormones and modulators of the genital system, Pregnadien derivatives.

**ATC code:** G03DB01

**Mechanism of action:** Dydrogesterone is an orally active progestogen which causes full secretory transformation of the estrogen-activated endometrium and therefore significantly reduces the increased risk of endometrial hyperplasia or carcinogenesis induced by estrogens. Dydrogesterone has no estrogenic, androgenic, thermogenic, anabolic or corticoid effects.

## 5.2. PHARMACOKINETICS PROPERTIES:

**Absorption:** Following oral administration, dydrogesterone film-coated tablets is rapidly absorbed. Maximum plasma concentration of about 3.2ng/ml and 57ng/ml are attained between 0.5 and 1.5 hours after dosing for the parent drug dydrogesterone and its active metabolite 20α-dihydrodydrogesterone (DHD) respectively. The total drug exposures across time (AUC) are about 9.1 and 220 ng.hr/ml for Dydrogesterone and DHD respectively. After a single dose, food delays the peak plasma concentration of dydrogesterone with approximately 1 hour, resulting in approximately 20% lower dydrogesterone peak plasma concentrations without affecting the extent of exposure to dydrogesterone and DHD. The observed effect of concomitant food intake on the peak plasma concentration of dydrogesterone is considered not clinically relevant. Therefore, ***DANILON®*** film-coated tablets can be taken without regards to food.

**Distribution:** After oral administration of dydrogesterone the apparent volume of distribution is large, being approximately 22,000 L. Dydrogesterone and DHD are more than 90% bound to plasma proteins.

**Metabolism:** Following oral administration, dydrogesterone is rapidly metabolized to DHD. The levels of the main active metabolite DHD peak at similar times as Dydrogesterone. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and $C_{max}$ ratios of DHD to dydrogesterone are approximately 25 and 20, respectively. The mean terminal elimination half-lives of both dydrogesterone and DHD is about 15 hours. A common feature of all metabolites characterized is the retention of the 4,6 diene-3-one configurations of the parent compound and the absence of 17α-hydroxylation. This explains the lack of estrogenic and androgenic effects of dydrogesterone.

**Elimination:** After oral administration of labeled dydrogesterone, on average 63% of the dose is excreted into the urine. The apparent total body clearance of dydrogesterone from plasma is high at approximately 20L/min Within 72 hours excretion is complete. DHD is present in the urine predominantly as the glucuronic acid conjugate.

**Dose and time dependencies:** The single and multiple dose pharmacokinetics are linear in the oral dose range of 2.5 to 20mg. Comparison of the single and multiple dose kinetics shows that the pharmacokinetics of dydrogesterone and DHD are not changed as a result of repeated dosing. Steady state conditions are generally reached after 3 days of treatment.

## 5.3. PRECLINICAL SAFETY DATA:

Non-clinical data obtained from conventional studies on single and repeated dose toxicity, genotoxicity and carcinogenic potential do not indicate any special hazard for humans. Reproductive toxicity studies in rats have shown an increased incidence of prominent nipples (between day 11 and day 19 of age)

and of hypospadias in the male offspring at high dosages not comparable to human exposure. The actual risk of hypospadias in humans cannot be determined in animal studies due to major species differences in metabolism between rats and humans. Limited safety data from animal studies suggest that dydrogesterone has a delaying effect on parturition. This is consistent with the progestogenic activity of dydrogesterone.

**Environmental risk assessment:** Environmental assessment studies have shown that dydrogesterone, may pose a risk to the aquatic environment.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS:

- Lactose Monohydrate
- Starch Corn
- HPMC (Methocel E5-LV)
- Colloidal Silicon Dioxide
- Magnesium Stearate
- Sheffcoat White

## 6.2. INCOMPATIBILITIES:

Not applicable

## 6.3. SHELF LIFE:

See expiry on the pack.

## 6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.

Do not store over 30°C and protect from heat, light and moisture.

Improper storage may deteriorate the medicine.

## 6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/PVC blister, pack size is 20’s.

## 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

This medicinal product may pose a risk to the aquatic environment. Medicines no longer required should not be disposed of via wastewater of household waste. Any unused product or waste material should be disposed of in accordance with local requirements or returned to the pharmacy.

## 6.7. DRUG PRODUCT SPECIFICATIONS:

BP Specs.

## 7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured for:
**SAMI Pharmaceuticals (Pvt.) Ltd.**
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
ML No. 000072

Manufactured by:
Platinum Pharmaceuticals(Pvt.) Ltd.
A-20, North Western Industrial Zone
Bin Qasim Karachi-75020, Pakistan
ML No.000415

## 8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

076057

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

20th September, 2013

## 10. DATE OF REVISION OF THE TEXT

# ڈینیلون® ٹیبلٹ

(ڈائیڈروجیسٹیرون)

## ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔