For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Dydrogesterone Tablets IP 10 mg

Dydetrogyl®

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dydrogesterone IP.....10mg

Excipients.....q.s.

Colour: Titanium Dioxide IP

DOSAGE FORM AND STRENGTH

Film coated tablets

CLINICAL PARTICULARS

Therapeutic Indications

Dydetrogyl is indicated for the following -

Progesterone Deficiencies

- Treatment of dysmenorrhoea
- Treatment of endometriosis
- Treatment of secondary amenorrhoea
- Treatment of irregular cycles
- Treatment of dysfunctional uterine bleeding
- Treatment of premenstrual syndrome
- 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.

Hormone Replacement Therapy

For treatment of women with intact uterus for the symptoms of estrogen deficiency as consequence of the menopause or after overectomy and for the prevention of post- menopausal osteoporosis.

Posology and Method of Administration

Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response.

Dysmenorrhoea

10 or 20 mg dydrogesterone per day from day 5 to day 25 of the Menstrual cycle.

Endometriosis

10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously.

Dysfunctional Uterine Bleeding

When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days.

For continuous treatment, 10 or 20 mg dydrogesterone per day should be given during the second half of the menstrual cycle. The starting day and the number of treatment days will depend on the individual cycle length.

Withdrawal bleeding occurs if the endometrium has been adequately primed with either endogenous or exogenous estrogen.

Secondary Amenorrhoea

10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.

Premenstrual Syndrome

10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length.

Irregular Cycles

10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length.

Threatened Miscarriage

An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30 mg per day until symptoms remit.

Habitual Miscarriage

10 mg dydrogesterone twice daily until the twentieth week of pregnancy.

Infertility due to Luteal Insufficiency

10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles.

Luteal Support as part of an Assisted Reproductive Technology (ART) Treatment 1 tablet of dydrogesterone 10 mg three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed.

Hormone Replacement Therapy (HRT)

- Continuous sequential therapy: An estrogen 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 estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12-14 days of estrogen therapy
- Depending on the clinical response, the dosage can subsequently be adjusted to 20 mg dydrogesterone per day

There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents aged 12-18 years has not been established. Currently available data are described in 'Undesirable effect and Pharmacodynamic properties', but no recommendation on a posology can be made.

Method of Administration

For oral use

For administration of higher dosages, the tablets should be taken evenly distributed over the day.

Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Known or suspected progestogen dependent neoplasms (e.g. meningioma)
- Undiagnosed vaginal bleeding
- Treatment for luteal support as part of an ART treatment should be discontinued upon diagnosis of abortion /miscarriage.
- Contraindications for the use of estrogens when used in combination with dydrogesterone

Special Warnings and Precautions for Use

Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Conditions Which Need Supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered:

- Porphyria
- Depression
- Abnormal liver function values caused by acute or chronic liver disease

Hormone Replacement Therapy

The following warnings and precautions apply when using dydrogesterone in combination with estrogens for HRT

See also the warnings and precautions in the product information of the estrogen preparation.

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favorable than in older women.

Medical Examination / Follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including appropriate imaging tools, e.g., mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Endometrial Hyperplasia and Carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods.

The addition of a progestogen such as dydrogesterone cyclically for at least 12 days per month / 28 day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomized women can prevent the excess risk associated with estrogen- only HRT.

Breast Cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestogen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-progestogen therapy: The randomized placebo-controlled trial, Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen- progestogen for HRT that becomes apparent after about 3 years. The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment. HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian Cancer

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests 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 trial suggest that use of combined HRTs may to associated a similar, or slightly smaller, risk.

Venous Thromboembolism

HRT is associated with a 1.3-3-fold risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later.

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients.

Generally recognized risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, 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 immobilization is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilized.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary Artery Disease (CAD)

There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen- progestogen or estrogen-only HRT.

Combined estrogen-progestogen therapy: The relative risk of CAD during use of combined estrogen-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 estrogen-progestogen use is very low in healthy women close to menopause but will rise with more advanced age.

Ischemic Stroke

Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age- dependent, the overall risk of stroke in women who use HRT will increase with age.

Excipients

This medicinal product contains Lactose monohydrate.

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

Drug Interactions

In vitro data show that the major metabolic pathway generating the main pharmacologically active metabolite 20a 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 iso-enzymes (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 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, an increased metabolism of dydrogesterone may lead to a decreased effect. In vitro studies have shown that dydrogesterone and DHD do not inhibit or induce CYP drug metabolizing enzymes at clinically relevant concentrations.

Use in Special Populations

Pregnant Women

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 the literature to be associated with an increased risk of hypospadias. 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.

Lactating Women

No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicates that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period.

Fertility

There is no evidence that dydrogesterone decreases fertility at therapeutic dose.

Effects on Ability to Drive and Use Machines

Dydrogesterone has minor influence on the ability to drive and use machines. Infrequently, dydrogesterone may cause mild somnolence and/or dizziness, especially within the first few hours after intake. Therefore, care should be taken when driving or using machines.

Undesirable Effects

The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are vaginal haemorrhage, migraines/ headache, nausea, vomiting, abdominal pain, menstrual disorders and breast pain/tenderness.

The following undesirable effects have been observed with the frequencies indicated below during clinical trials using dydrogesterone (n=3483) in indications without estrogen treatment, in two company sponsored interventional clinical trials in luteal support as part of an ART treatment using dydrogesterone (n=1036) and from spontaneous reporting. Frequencies are based on the most conservative approach.

MedDRA system organ class	Very common ≥ 1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Neoplasms benign, malignant and unspecified (incl.cysts and polyps)				Increase in size of progestogen dependent neoplasms (e.g., meningioma)#
Blood and the lymphatic system disorders				Haemolytic anaemia#
Psychiatric disorders			Depressed mood	
Immune system disorders				Hypersensitivity
Nervous system disorders		Migraines/ headache	Dizziness	Somnolence
Gastrointestinal disorders		Nausea, Vomiting, Abdominal pain		
Hepatobiliary disorders			Hepatic function abnormal (with Jaundice, Asthenia or Malaise, and Abdominal pain)	
Skin and subcutaneous tissue disorders			Dermatitis allergic (e.g. rash, pruritus, urticaria)	
Reproductive system and breast disorders	Vaginal haemorrhage,	Menstrual Disorders (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Breast pain/ tenderness		Breast swelling
General disorders and administration site conditions				Oedema
Investigations		Weight increased		

Undesirable effects from spontaneous reporting which have not been observed in clinical trials have been attributed to the frequency 'rare' based on the fact that the upper limit of the 95% confidence interval of the frequency estimate is not higher than 3lx where x =3483 (total number of subjects observed in clinical trials).

Undesirable Effects in Adolescent Population

Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults.

Undesirable Effects that are Associated with an Estrogen-progestogen Treatment

(see the product information of the estrogen preparation):

- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary artery disease, ischemic stroke

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

Overdose

Limited data are available with regard to overdose in humans. Dydrogesterone was well tolerated after oral dosing (maximum daily dose taken to date in humans 360 mg). There are no specific antidotes and treatment should be symptomatic. This information is also applicable for overdose in children.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Dydrogesterone is an orally-active progestogen which produces a complete secretory endometrium in an estrogen-primed uterus thereby providing protection against the increased risk for endometrium hyperplasia and/or carcinogenesis induced by estrogens. It is indicated in all cases of endogenous progesterone deficiency. Dydrogesterone has no estrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity.

Pharmacodynamic Properties

Clinical efficacy and safety

Lotus I and Lotus II clinical study(s) confirmed the following:

A Double-Blind, Double-Dummy, Randomized, Two-arm, Multi-center Study Comparing the Efficacy, Safety, and Tolerability of Oral Dydrogesterone 30 mg daily versus Intravaginal Micronized Progesterone Capsules 600 mg daily for Luteal Support in In- Vitro Fertilization (LOTUS I).

A Randomized, Open-label, Two-arm, Multi-center Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg daily versus Crinone 8% intravaginal progesterone gel 90 mg daily for Luteal Support in In Vitro Fertilization (LOTUS II).

The primary objective of non-inferiority of oral dydrogesterone compared to intravaginal micronized progesterone in terms of the presence of fetal heartbeats at 12 weeks gestation (10 weeks pregnancy) was achieved.

In the studied patient population, pregnancy rates at 12 weeks gestation (pregnancy week 10) were 37.6% and 33.1% (LOTUS I) and 36.7% and 34.7% (LOTUS II). The difference in the pregnancy rate between the two groups was 4.7 (95% CI, -1.2; 10.6) (LOTUS I) and 2.0 (95% CI, -4.0; 8.0) (LOTUS II).

Within the safety sample of 1029 subjects (LOTUS I) and 1030 subjects (LOTUS II) with at least one dose of study medication administered, the incidence of the most frequently reported TEAE was similar between the two treatment groups.

Due to the nature of the studied patient population/indication a number of early abortions/ miscarriages are expected; especially until 12 weeks gestation (pregnancy week 10) as the expected pregnancy rate at this time point is about 35%.

The safety profile observed both LOTUS studies as expected taking into account the well-established safety profile of dydrogesterone and the treatment population/ indication.

Adolescent population

Limited clinical trial data indicate that dydrogesterone is efficacious in relieving symptoms of dysmenorrhoea, premenstrual syndrome, dysfunctional uterine bleeding and irregular cycles in the population of patients younger than 18 years of age in a similar manner as in the adult population.

Pharmacokinetic Properties

Absorption

Following oral administration, dydrogesterone is rapidly absorbed with a T_{max} between 0.5 and 2.5 hours. The absolute bioavailability of dydrogesterone (oral 20 mg dose versus 7.8 mg intravenous infusion) is 28%.

The following table provides pharmacokinetic parameters of dydrogesterone (D) and 20-α-dihydrodydrogesterone (DHD) after single dose administration of 10 mg dydrogesterone -

	D	DHD
Cmax (ng/mL)	2.1	53.0
AUC_{inf} (ng.h/ mL)	7.7	322.0

Distribution

After intravenous administration of dydrogesterone the steady-state volume of distribution is approximately 1400 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 about 1.5 hours postdose. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and Cmax ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively. Mean terminal halflives of dydrogesterone and DHD vary between 5 to 7 and 14 to

17 hours, respectively. A common feature of all metabolites characterised is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17a-hydroxylation. This explains the lack of estrogenic and androgenic effects of dydrogesterone.

Elimination

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. Total plasma clearance is 6.4 L/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

2.5 to 10 mg. 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 was reached after 3 days of treatment.

NON-CLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Non-clinical data obtained from conventional studies on single and repeated dose toxicity, genotoxicity and carcinogenic potential reveal no special hazard for humans. Reproduction 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 animal safety data suggest that dydrogesterone has prolongating effects on parturition, which is consistent with its progestogenic activity.

DESCRIPTION

White to off-white, round shaped, biconvex, film coated tablets, plain on both sides

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable

Packaging Information

Dydetrogyl is available as Alu-PVC Blister of 1x10 or 2x2 tablets packed in carton along with insert

Storage and Handling Instructions

Store at a temperature not exceeding 25°C. Protect from light.

PATIENT COUNSELLING INFORMATION

Patient should not take Dydrogesterone tablets

- in case of a tumour that is made worse by progestogens (such as meningioma)
- in case of irregular or unusually heavy periods that the doctor does not already know about
- if patient is allergic (hypersensitive) to any of the ingredients of this medicine
- If patient gets unexpected vaginal bleeding or spotting an appointment should be made to see the doctor.

Patient should tell the doctor if she is taking or have recently taken any other medicines. This includes medicines obtained without a prescription or herbal medicines. In particular, the following medicines may lower the effect of Dydrogesterone and lead to bleeding or spotting -

- medicines for fits (epilepsy) such as phenobarbital, phenytoin or carbamazepine
- medicines for infection such as rifampicin, rifabutin, nevirapine, efavirenz
- medicines for HIV infection (AIDS) such as ritonavir or nelfinavir
- medicines for diabetes such as insulin
- herbal medicines containing St John's Wort (Hypericum perforatum), valerian root, sage, or ginkgo biloba

Taking Dydrogesterone

- Swallow the tablet with water
- Can take the tablet with or without food.
- If the patient has to take more than one tablet, they should be spread evenly over the day. For example, one tablet in the morning and one in the evening.
- The tablet should be taken at the same time each day. This will make sure that there is a constant amount of the medicine in the body.

If you take more Dydrogesterone or forget to take Dydrogesterone than you should consult your doctor.

- This medicine prescribed for a particular patient shouldn't be passed on to the others. It may harm them, even if their symptoms are the same.
- If any of the side effects gets serious, or if the patient notices any side effects not listed above, the doctor needs to be informed

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

Note: This prescribing information is applicable for India Market only

DATE OF REVISION

March 2023.