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

DYDROPREG

1. GENERIC NAME

Dydrogesterone Tablets I.P. 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dydrogesterone I.P. ……..10 mg

Excipients ……..q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Starch, Hypromellose, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry White Y-1-7000.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Tablet

Strength: 10 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Luteal support as part of an assisted reproductive technology (ART) treatment.

4.2 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.

Pre-menstrual syndrome: 10 mg Dydrogesterone twice daily starting with the secondhalf 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 abortion: An initial dose of up to 40 mg Dydrogesterone may be given followed by 20 or 30 mg per day until symptoms remit.

Habitual abortion: 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.

Hormone replacement therapy:

- **Continuous sequential therapy:** An estrogen is dosed continuously and one tablet of 10 mg 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 'Adverse Reactions and 'Pharmacodynamic Properties', but no recommendation on a posology can be made.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Known or suspected progestogen dependent neoplasms (e.g. meningioma)
- Undiagnosed vaginal bleeding
- If used to prevent endometrial hyperplasia (in women using estrogens) : Contraindications for use of oestrogens in combination with progestagens, such as Dydrogesterone

4.4 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

Other Conditions

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

The following warnings and precautions apply when using Dydrogesterone in Combination with estrogens for hormone replacement therapy (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 favourable 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 (see 'Breast cancer' below). 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

Long-term use of oestrogens without addition of progestagens increases the change of endometrial hyperplasia and endometrial carcinoma in women with a uterus. This risk may largely be prevented by combining the oestrogen therapy for at least 12 days per cycle with a progestagen, such as Dydrogesterone.

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. 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 detection of breast cancer.

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 trial suggest that use of combined HRTs may be 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/m2), 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 counselling 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 initiatingtherapy, 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 reported randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogenprogestogen or estrogen-only HRT.

Combined oestrogen-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.

Cerebrovascular accident (CVA)

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 agedependent, the overall risk of stroke in women who use HRT will increase with age.

4.5 Drug Interactions

In vitro data show that 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 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, and Carbamazepine), anti-infectives (e.g., Rifampicin, Rifabutin, Nevirapine, Efavirenz) and herbal preparations containing e.g. St John's Wort (Hypericumperforatum), 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.

4.6 Use in special population

Pregnancy:

It is estimated that more than 9 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.

Breast feeding

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.

4.7 Effects on ability to drive and use machines

Dydrogesterone has a slight effect on ability to drive and to use machinery. In rare cases Dydrogesterone may cause somnolence and/or dizziness, in particular during the first couple of hours after taking it. Caution is therefore advised when driving and operating machinery.

4.8 Undesirable effects

Organ class according to MedDRA database	**Common ≥1:100, <1:10**	**Uncommon ≥1:1,000, <1:100**	**Rare ≥1:10,000, <1:1,000**
Neoplasms, benign, Malignant and nonspecified (including cysts and polyps)			Growth of progestogendependent neoplasms (e.g. Eningioma)*
Blood and			Haemolytic

lymphatic system disorders			anaemia*
Psychiatric disorders		Depression	
Immune system disorders			Hypersensitivity
Nervous system disorders	Migraine / Headache	Dizziness	Somnolence
Gastrointestinal disorders	Nausea	Vomiting	
Hepatobiliary disorders		Disturbed liver function (with Icterus, Asthenia or Malaise, and abdominal pain)	
Skin and subcutaneous tissue disorders pruritus, Urticaria)		Allergic dermatitis (e.g. rash,	Angiooedema*
Reproductive system and breast disorders	Disturbed menstruation (including Metrorrhagia, menorrhagia, Oligo-/amenorrhoea, Dysmenorrhoea and Irregular menstruation) Painful/ sensitive breasts		Swelling of the breasts
General disorders and administration site conditions			Oedema
Investigations		Weight gain	

*** Adverse effects reported spontaneously**

Undesirable effects that are associated with an estrogen-progestogen treatment (see also 'Warnings and Precautions' and 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

Dydrogesterone is a substance with very low toxicity. Nausea, vomiting, lethargy and dizziness are symptoms which may theoretically occur in the event of an overdose. There are no known cases in which an overdose of Dydrogesterone led to harmful effects.

Treatment

Specific treatment is clearly not necessary. In case of overdose symptomatic treatment may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacodynamic properties

Dydrogesterone has no estrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity. Dydrogesterone does not suppress ovulation.

5.3 Pharmacokinetic properties

Absorption

After oral administration Dydrogesterone is rapidly absorbed with a Tmax of between 0.5 and 2.5 hours. The absolute biological availability of Dydrogesterone (20 mg oral dose versus 7.8 mg intravenous infusion) is 28%. The following tables gives the pharmacokinetic parameters of Dydrogesterone (D) and 20α Dihydrodydrogesterone (DHD) after administration of a single dose of 10 mg

Dydrogesterone:

	D	**DHD**
Cmax (ng/mL)	2.1	53.0
AUCinf (ng·h/mL)	7.7	322.0

Distribution

After intravenous administration of Dydrogesterone the steady-state distribution volume is around 1400 l. More than 90% of Dydrogesterone and DHD are bound to plasma-proteins.

Metabolism

After oral administration Dydrogesterone is quickly metabolised to DHD. The plasma levels of the main active metabolite DHD show a peak around 1.5 hours after administerin the dose. The plasma levels of DHD are substantially higher than the related medicinal product. The AUC and Cmax ratios of DHD and Dydrogesterone are of the order of magnitude of respectively 40 and 25. The mean terminal half-life of Dydrogesterone and DHD varies from respectively 5 to 7 and 14 to 17 hours. A common characteristic of all characterised metabolites is the retention of the 4,6-diene-2-one configuration of the original product and the absence of 17α hydroxylation. This explains the absence of oestrogenic and androgenic effects of Dydrogesterone.

Elimination

After oral administration of labelled Dydrogesterone on average 63% of the dose is excreted in the urine. The total plasma clearance is 6.4 l/minute. Within 72 hours the excretion is complete, DHD is present in the urine mainly as the conjugated glucuronic acid.

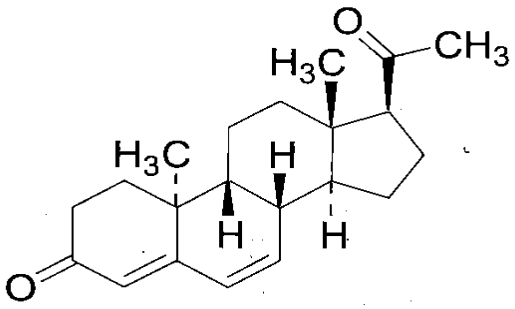
6. NON-CLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Non-clinical data obtained during conventional investigation into the toxixcity of single and repeated doses, genotoxicity and the carcinogenic potential do not show any special risks for humans. Research into the toxic effects on the reproduction of rats shows for high doses (>80 times the human exposure) an increased incidence of erect nipples (during days 11-19 of the lactation period) and of hypospadia in male rats. The clinical relevance of these observations is not known. The limited data on safety in animals indicate that Dydrogesterone has an extending effect on delivery, which corresponds with the progestogenic action.

7. DESCRIPTION

Dydrogesterone is 9β, 10α-pregna-4, 6-diene-3,20-dione. The empirical formula of Dydrogesterone is $C_{21}H_{28}O_2$ and its molecular weight is 312.5. Its structural formula is:



Dydrogesterone is a white to off-white crystalline powder. It is freely soluble in chloroform, soluble in acetone, sparingly soluble in ethanol (95 percent) and in methanol; slightly soluble in ether, practically insoluble in water.

DYDROPREG are white to off-white colour, circular shape, coated tablet with breakline on one side & other side plain.

The excipients used are Lactose Monohydrate, Starch, Hypromellose, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry White Y-1-7000.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Do not use later than the date of expiry.

8.3 Packaging Information

DYDROPREG is available in Blister strip of 10 tablets.

8.4 Storage and handling instructions

- Store at temperature not exceeding 25°C. Protect from light.
- Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

DYDROPREG

Dydrogesterone Tablets I.P. 10 mg

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What DYDROPREG is and what it is used for

DYDROPREG is a film coated tablet contains Dydrogesterone and it’s used as Luteal support as part of an assisted reproductive technology (ART) treatment.

9.2. What you need to know before you take DYDROPREG.

Talk to your doctor before taking DYDROPREG.

- If you are allergic to DYDROPREG or any of the other ingredients of this medicine.

Do not take DYDROPREG if you:

- have kidney disease or kidney failure.
- have reduced adrenal gland function (adrenal insufficiency).
- have or have had cervical cancer or any cancer that is sensitive to female hormones.
- have liver disease, including liver tumors.
- have unexplained vaginal bleeding.
- Tell your healthcare provider if you have or have had any of these conditions. Your healthcare provider can suggest a different method of birth control.

Warnings and precautions

Before initiating DYDROPREG 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 DYDROPREG and ceasing the treatment should be considered:

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

Other Conditions

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

9.3. How to take DYDROPREG.

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

If you take more DYDROPREG than you should:
If you had taken too many DYDROPREG tablets contact your doctor or nearest hospital for advice.
If you forget to take DYDROPREG.
If you forget to take a dose of DYDROPREG, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking DYDROPREG.
Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

Blood and lymphatic system disorders: Haemolytic anaemia

Psychiatric Disorders: depression

Immune system disorders: Hypersensitivity

Nervous system disorders: Migraine / Headache, Dizziness, Somnolence.

Gastrointestinal disorders: Nausea and Vomiting

Hepatobiliary disorders: Disturbed liver function (with Icterus, Asthenia or Malaise, and abdominal pain)

Skin and subcutaneous tissue disorders pruritus, Urticaria : Allergic dermatitis (e.g. rash, Angiooedema*)

Reproductive system and breast disorders: Disturbed menstruation (including Metrorrhagia, menorrhagia, Oligo- /amenorrhoea, Dysmenorrhoea and Irregular menstruation) Painful/ sensitive breasts, Swelling of the breasts.

General disorders and administration site conditions: Oedema

Investigations: weight gain

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5. How to store DYDROPREG.

- Store at temperature not exceeding 25°C. Protect from light.
- Keep out of reach of children.

10. DETAILS OF MANUFACTURER

Manufactured in India by:

Emcure Pharmaceuticals Ltd.

At: Plot No. 56-57, Sectore-6A,

I.I.E. (SIDCUL), Ranipur (BHEL),

Haridwar-249403, Uttarakhand, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg. Lic. No.: 11/UA/LL/SC/P-2020 issued on 13.05.2020

12. DATE OF REVISION

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ DYDROPREG 10mg /JAN-22/01/PI