For the use of a Registered Medical Practitioner only (Gynecologist Only)

1. **Generic Name and Brand Name:**
   Dydrogesterone Modified Release Tablets 20 mg
   Duphaston® OD 20

2. **Qualitative and Quantitative Composition:**
   Each film coated modified release tablet contains:
   Dydrogesterone I.P. 20 mg
   Excipients …… q.s.

3. **Dosage Form & strength**
   Film coated modified release tablets,
   20 mg of Dydrogesterone.

4. **Clinical particulars**

4.1 Therapeutic Indication

It is indicated in cases where progesterone supplement is needed.

4.2 Posology and method of administration

Posology

Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response. The dosage of 20mg once daily, is recommended to be prescribed in the management of the following conditions requiring this dosage:

Dysmenorrhoea: 20 mg dydrogesterone per day from day 5 to day 25 of the Menstrual cycle.

Endometriosis: 20 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 mg dydrogesterone per day is to be given for up to 10 days.

For continuous treatment, 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: 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: 20 mg dydrogesterone 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: 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 20mg per day until symptoms remit.

Habitual miscarriage: 20 mg dydrogesterone daily until the twentieth week of pregnancy.

Infertility due to luteal insufficiency: 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.

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.

Method of Administration:
For oral use.
The tablet should not be crushed / chewed / broken / split before administration.

4.3 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

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 glucose-galactose malabsorption should not take this medicine.

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.

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, 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.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

The information in this section is based on information available for the immediate release formulation.
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 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 (see section 6.1).

Dydrogesterone can be used during pregnancy if clearly indicated.

Breastfeeding
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 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.

4.8 Undesirable effects

The information in this section is based on information available for the immediate release formulation. Based on data from immediate release formulation 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)	Angioedema[#]

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 3/x 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.

4.9 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.

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. Dydrogesterone has no estrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity.

5.2 Pharmacodynamic Properties

Clinical efficacy and safety of modified release formulation:

A bioequivalence study confirmed that dydrogesterone MR tablets 20 mg administered once daily was bioequivalent to the 10 mg IR formulation administered twice daily for AUC parameter. This was followed by Phase III Clinical study with modified release formulation in 230 patients with endometriosis:

A Prospective, Randomized, Single-blind, Single-dummy, Two-arm, Multicentric Study To Assess the Efficacy And Safety Of Dydrogesterone Modified Release Tablets 20 mg OD Compared to Dydrogesterone 10 mg IR (BID) in the Management Of Endometriosis

Both the treatment arms showed statistically significant change in VAS score from baseline visit to end of study visit with a mean change of -38.5(13.79) and -39.4(16.27) with Dydrogesterone modified release tablets 20 mg OD and Dydrogesterone 10 mg IR BID, respectively. The primary objective of the study was achieved based on determination of non-inferiority of dydrogesterone 20 mg MR OD to dydrogesterone 20 mg IR BID in the management of endometriosis associated chronic pelvic pain. ,

HR QoL- SF-20 scores were also comparable in dydrogesterone 20 mg MR OD and between dydrogesterone 20 mg IR BID arms in all six domains of Pain, Health perception, Mental health, Physical functioning, Role functioning and Social functioning. There was also no clinically relevant difference noted between dydrogesterone 20 mg MR OD and dydrogesterone 20 mg IR BID arms for analgesic usage during the study by the subjects.

Within the safety sample of 229 subjects with at least one dose of study medication administered, the nature of the most frequently reported TEAE was similar between the two treatment groups. Gastrointestinal disorders (i.e. Diarrhea, Abdominal Pain, Nausea and Vomiting) & Nervous system disorders (i.e. headache and Dizziness) were the most commonly affected SOCs in both treatment arms.
The safety profile observed in this study under 20 mg once-daily modified release formulation for treatment of endometriosis can be considered similar to the safety profile observed under twice-daily 10 mg immediate release formulation.

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.

5.3 Pharmacokinetic properties: Based on data from immediate release formulation of dydrogesterone:

Absorption:
Following oral administration, dydrogesterone film-coated tablets is rapidly absorbed . Maximum plasma concentrations of about 3.2 ng/ml and 57 ng/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.

Distribution:
After oral administration of dydrogesterone the apparent volume of distribution is large, being approximately 22000 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 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 characterised is the retention of the 4,6 diene-3-one configuration 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 labelled 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 20 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 conditions are generally reached after 3 days of treatment.

An open-label, balanced, randomized, two-treatment, two sequence, two period, two way cross-over, oral dose, bioequivalence study of single dose of Dydrogesterone Modified Release Tablet 20 mg of Abbott India Ltd and Duphaston® Tablets 10 mg of Abbott India Ltd. administered twice daily in healthy, adult, women subjects under fasting conditions was conducted. The study demonstrated the modified release tablets are bioequivalent to the immediate release tablets and were well tolerated.

6. Nonclinical properties

6.1 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 (see also section 4.6) Limited animal safety data suggest that dydrogesterone has prolongating effects on parturition, which is consistent with its progestogenic activity.

7. Description

White or almost white, round, biconvex tablets with embossing of Abbott “a” on one side.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage and handling instructions

Refer Pack

9. Patient Counseling Information

- Patient should not take Duphaston:
  - 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 Duphaston 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 Duphaston
  • Swallow the tablet with water
  • 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 Duphaston or forget to take Duphaston 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.

10. Details of manufacturer
MANUFACTURED BY
Abbott India Limited
At: 45, Mangalam Main Road, Mangalam Village,
Villianur Commune, Puducherry- 605110, India.

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11. Details of permission or licence number with date
Mfg. License No. 13 23 3725, dated 01-Feb-25

12. Date of revision
Version No. 7.0, dated 21st March 2025

For product complaints and queries please write to **webmasterindia@abbott.com**