SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nalvee 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg dydrogesterone.

Excipient(s) with known effect: each tablet contains 111.10 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

Round, biconvex, white film-coated tablet marked with “L1” on one side and without marking on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nalvee 10 mg is used for women with:

- **Progesterone insufficiencies:** Treatment of dysmenorrhoea, endometriosis, irregular menstrual cycles and pre-menstrual syndrome.
- **Hormone replacement therapy:** Dydrogesterone is used to supplement an estrogen treatment in non-hysterectomised women with symptoms due to natural

onset of or surgically induced menopause. In the context of hormone replacement therapy, it counteracts the estrogen influence on the endometrium.

- **Dysfunctional bleeding or secondary amenorrhoea:** The drug may be used with an estrogen in the management of these conditions.

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:

Dysmenorrhoea:

10 mg of dydrogesterone twice a day from day 5 to 25 of the cycle.

Endometriosis:

10 mg of dydrogesterone two to three times daily from day 5 to 25 of the cycle, or continuously.

Irregular menstrual cycles:

10 mg of dydrogesterone twice a day from day 11 to 25 of the cycle.

Pre-menstrual syndrome:

10 mg of dydrogesterone twice a day from day 12 to 26 of the cycle. The dosage may be increased if necessary.

Hormone replacement therapy: i.e. as supplement in estrogen treatment in non-hysterectomised women with symptoms due to natural onset of or surgically induced menopause:

- Continuous sequential therapy: continuous use of an estrogen; sequential supplementation of 10 mg dydrogesterone during the last 14 days of each 28-day cycle
- Cyclical treatment: cyclic use of an estrogen with a treatment-free period, usually 21 days on and 7 days off treatment. For the last 12-14 days of estrogen use, 10 mg of dydrogesterone is supplemented.
- Depending on the clinical response, the dosage may be adjusted to 20 mg dydrogesterone daily in the course of the treatment.

Dysfunctional uterine bleeding:

When treatment is started to arrest a bleeding episode 10 mg of dydrogesterone twice a day for five to seven days.

For continuous treatment 10 mg of dydrogesterone twice a day from day 11 to day 25 of the cycle.

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

Secondary amenorrhoea:

10 mg of dydrogesterone twice a day from day 11 to 25 to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.

There is no relevant use for 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 section 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

For oral use.

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 listed in section 6.1
- 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.

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.

Condition which need supervision

Patients should be closely monitored if any of the following situations or conditions are present or have previously been present or have worsened during pregnancy or previous hormone treatment. It should be considered that these situations or conditions may recur or worsen during therapy with dydrogesterone and discontinuation of treatment should be considered:

- Porphyria
- Depression
- Pathological liver function values caused by acute or chronic liver disease
- Cholestatic jaundice and/or pruritus

Dydrogesterone does not generally appear to affect blood pressure in normotensive women. However, if persistent clinically significant hypertension develops during the use of dydrogesterone, it is advisable to discontinue dydrogesterone and to treat the hypertension.

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)

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

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 favourable than in older women.

Medical examinations/follow-up

Before starting or resuming HRT, a complete personal and family medical history should be obtained. The medical examination (including pelvic and breast examination) should be guided by information based on this medical history, as well as on the contraindications and precautions. Regular follow-up examinations are recommended during treatment, the frequency and nature of which are individual to each woman's risk. Women should be advised what changes in the breasts should be reported to their doctor (see 'Breast cancer' below). Examinations, including appropriate imaging methods such as mammography, should be carried out in accordance with currently accepted screening practice, adapted to the clinical needs 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 estrogen monotherapy.

Adding a progestogen such as dydrogesterone cyclically for at least 12 days per month/28-day cycle or continuous combined estrogen-progestogen therapy in women with a uterus compensates for the additional risk posed by estrogen monotherapy.

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.

Combined estrogen and progestogen therapy: The randomised placebo-controlled trial, Women's Health Initiative Study (WHI), and a meta-analysis of prospective 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 (1-4) years (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to age-related baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially combined treatment with estrogen and progestogen, increases the density of mammographic findings, which may adversely affect the radiological detection of breast cancer.

Risk of ovarian cancer

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women who take HRT containing estrogen-only or an estrogen-progestogen combination, which becomes apparent within 5 years of use and gradually decreases after discontinuation.

Some other studies, including the WHI trial, suggest that the use of combination HRT may be associated with a similar or slightly lower 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 (see section 4.8).

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 > 30 kg/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

Randomised, controlled trials have provided no evidence of protection against myocardial infarction in women, who were taking combination HRT with estrogen and progestogen or estrogen alone, regardless of whether or not they have coronary artery disease.

Combined estrogen and progestogen therapy

The relative risk of coronary artery disease is slightly increased with combined estrogen-progestogen HRT. Since the baseline risk of coronary artery disease is largely age-dependent, the number of incident cases of coronary artery disease induced by estrogen-progestogen combination HRT is very low in healthy women shortly after menopause. However, the number increases with 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 (see section 4.8).

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 forms of interaction

In vitro data show that the pharmacologically active metabolite 20α dihydrodydrogesterone (DHD) is formed in the human cytosol by metabolic degradation by aldo-keto-reductase (AKR 1C). In addition to cytosolic metabolism, metabolic transformations occur via cytochrome P 450 (CYP) isoenzymes - almost exclusively via CYP3A4, resulting in several secondary metabolites. The main active metabolite DHD is metabolically transformed by CYP3A4.

Therefore, the metabolism of dydrogesterone and DHD may be increased when used concomitantly with substances known to induce CYP enzyme activity. These substances include anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine), preparations for the treatment of infections (e.g., rifampicin, rifabutin, nevirapine, efavirenz) and herbal preparations containing St John's wort (*Hypericum perforatum*), sage or ginkgo biloba. Although ritonavir and nelfinavir are known to act as potent inhibitors of cytochrome enzymes, they have enzyme-inducing properties when used concomitantly with steroid hormones.

Clinically, increased dydrogesterone metabolism may lead to reduced effect.

In vitro studies have shown that dydrogesterone and DHD at clinically relevant concentrations do not have an inhibitory or inducing effect on drug-metabolizing CYP enzyme (cytochrome P450) systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nalvee 10 mg is not authorised for use in pregnancy.

It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there is no evidence of any harmful effect of dydrogesterone use during pregnancy.

The literature suggests that some progestogens are associated with an increased risk of hypospadias. Due to confounders during pregnancy, no definitive conclusion can be drawn on the actual contribution of these progestogens on the risk of hypospadias. Clinical trials in which a limited number of women in early pregnancy were treated with dydrogesterone showed no increased risk. No other epidemiological data are yet available.

Observed 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, therefore indicating little relevance to clinical use (see section 5.3).

Breastfeeding

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, Nalvee 10 mg should not be taken while breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Nalvee 10 mg 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 following undesirable effects have been observed in women under treatment with dydrogesterone (n=3,483) with the frequencies indicated below during clinical trials in indications without estrogen use and from spontaneous reporting:

MedDRA System Organ Classes	**Common** (>1/100 to <1/10)	**Uncommon** (>1/1,000 to <1/100)	**Rare** (>1/10,000 to <1/1,000)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Increase in size of progestogen dependent tumours (e.g. meningioma)*
Blood and lymphatic system disorders			Haemolytic anaemia*
Psychiatric disorders		Depressed mood	
Immune system disorders			Hypersensitivity reactions
Nervous system disorders	Headache, Migraine	Dizziness	Somnolence
Gastrointestinal disorders	Nausea	Vomiting	
Hepatobiliary disorders		Hepatic function abnormal (with asthenia or malaise, jaundice and abdominal pain)	
Skin and subcutaneous tissue disorders		Dermatitis allergic (e.g. rash, urticaria, pruritus)	Angioedema*

Reproductive system and breast disorders	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 gain	

* Adverse reactions from spontaneous reporting that were not observed in clinical trials are designated as "rare" based on the fact that the upper limit of the 95% confidence interval of the frequency estimate is no greater than 3/x, where x=3,483 (total number of subjects followed in clinical trials).

Undesirable effects in adolescents

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

Adverse reactions associated with combined treatment of estrogen and progestogen (see also section 4.4 and the information on the estrogen-containing product)

- Breast cancer, endometrial hyperplasia, endometrial cancer, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary disease, ischaemic 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 asked to report any suspected adverse reactions via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The available data with regard to overdose in humans are limited.

Dydrogesterone has been well tolerated after oral administration (maximum daily dose in humans to date has been 360 mg). No specific antidotes are known. Treatment should be symptomatic. This information also applies to overdoses in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, Pregnadien derivatives. ATC code: G03DB01

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.

Adolescents

Limited data from clinical trials indicate that the effect of dydrogesterone in relieving symptoms of dysmenorrhoea, premenstrual syndrome, dysfunctional uterine bleeding, and irregular cycles in patients under 18 years of age is comparable to the effect in adults.

5.2 Pharmacokinetic properties

Absorption

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

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

	D	DHD
C_{max} (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 1,400 L.

Dydrogesterone and DHD are more than 90% bound to plasma proteins.

Biotransformation

Following oral administration, dydrogesterone is rapidly metabolized to DHD. The levels of the main active metabolite DHD peak about 1.5 hours post dose. The plasma level of DHD is substantially higher as compared to the parent drug. The ratios of DHD to dydrogesterone for AUC (area under the concentration-time-curve) and C_{max} (maximum plasma concentration) are in the order of 40 and 25, respectively. Mean terminal half-lives 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 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. 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.

Pharmacokinetic/pharmacodynamic relationships

The single and multiple dose pharmacokinetics are linear in the oral dose range 2.5 to 10 mg. Comparison of the kinetics with each other shows that the pharmacokinetics of dydrogesterone and DHD do not change with repeated dosing. Steady state was 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 (see also section 4.6).

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

Core:

Lactose monohydrate

Hypromellose

Maize starch

Silica, colloidal anhydrous

Magnesium Stearate

Film coating:

Hypromellose

Macrogol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require special storage conditions.

6.5 Nature and contents of container

Nalvee is packed in blister packs consisting polyvinyl chloride (PVC) coated polyvinylidene chloride (PVDC) blisters heat-sealed aluminium (Alu) foil.

Package contents: 10, 20 and 28 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

Gyömrői út 19-21,

1103 Budapest,

Hungary

8 MARKETING AUTHORISATION NUMBER(S)

PL 04854/0198

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2024

10 DATE OF REVISION OF THE TEXT

12/12/2025