SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Dydrogesteron Lotus 10 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10mg dydrogesterone.

Excipient with known effect
106.9 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

A round, biconvex, white to off-white film-coated tablet (appox 7.1 mm in diameter), debossed with "711" on one side and plain on another.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Irregular menstrual cycles
- Endometriosis
- Dysmenorrhoea
- Secondary amenorrhoea
- Dysfunctional uterine bleeding
- Infertility as a result of corpus luteum insufficiency
- Support of the luteal phase as part of an ART (Assisted Reproductive Technology) procedure
- Threatened miscarriage as a result of progesterone deficiency
- Habitual miscarriage as a result of progesterone deficiency

As a cyclical addition to oestrogen replacement therapy in postmenopausal women with an intact uterus for prevention of endometrial hyperplasia.

4.2 Posology and method of administration

Posology
For treatment with Dydrogesterone Lotus, the following dosage regimens are recommended. Dosages, treatment schedule and duration of treatment may be adapted to the severity of the condition and the clinical response.

Irregular menstrual cycles
1 tablet per day, from day 11 to 25 of the cycle. With this dosing scheme, it is possible to achieve a menstrual cycle lasting 28 days.

Endometriosis
1 to 3 tablets per day from days 5 to 25 of the cycle or for the entire cycle. Dosages of 10 mg several

times daily should be given as divided doses throughout the day. It is recommended that treatment is started at the highest dosage.

Dysmenorrhoea
1 to 2 tablets per day from days 5 to 25 of the cycle. Dosages of 10 mg several times daily should be given as divided doses throughout the day. It is recommended that treatment is started at the highest dosage.

Infertility as a result of corpus luteum insufficiency
1 tablet per day from day 14 to 25 of the cycle
Treatment should be continued for at least 3 consecutive cycles. It is advisable to continue this treatment for the first months of any pregnancy at dosages as indicated for habitual miscarriage.

Support of the luteal phase during an ART (Assisted Reproductive Technology) procedure
3 tablets per day, starting on the day of oocyte retrieval, for 12 weeks during pregnancy.

Threatened miscarriage
Starting dose: 4 tablets at once, followed by 1 tablet every 8 hours.
If symptoms do not resolve or recur during treatment, 2 tablets should be administered every 8 hours
The effective dose should be maintained for one week after resolution of symptoms; it can then be gradually reduced. If symptoms recur, treatment should be resumed immediately at the effective dose.

Habitual miscarriage
1 tablet twice daily up to week 20 of pregnancy, after which the dose can be gradually reduced.
Treatment should preferably be started before conception.
If signs of threatened miscarriage occur during treatment, treatment should be continued as described for that indication.

Dysfunctional uterine bleeding
When treatment is started to arrest a bleeding episode, 1 tablet twice daily should be taken for 5 to 7 days. Blood loss decreases sharply within a few days. A few days after the end of this treatment, a heavy withdrawal bleed occurs and the patient should be warned about this.
For continuous treatment a prophylactic dose of 1 tablet per day from days 11 to 25 of the cycle, if necessary combined with an oestrogen for 2 to 3 cycles. Thereafter, treatment can be discontinued, in order to check whether the patient's cycle has returned to normal.

Secondary amenorrhoea
1 to 2 tablets per day from days 11 to 25 of the cycle to give optimum secretory transformation of the endometrium, which has been adequately prepared with an endogenous or exogenous oestrogen.

Prevention of endometrial hyperplasia in postmenopause
In each 28-day cycle of oestrogen therapy, oestrogen alone is used for the first 14 days and 1 or 2 dydrogesterone 10 mg tablets are taken once daily in addition to oestrogen therapy for the following 14 days. At a dosage of 2 dydrogesterone 10 mg tablets per day, the tablets should be taken in divided doses throughout the day. Usually, withdrawal bleeding occurs during the use of dydrogesterone.

Administration of combined oestrogen/progestogen therapy in postmenopausal women should be restricted to the lowest effective dose and the shortest duration consistent with treatment goals and risks for the individual woman and should be periodically evaluated (see section 4.4).

Management of missed dose(s)
If a dose has been missed, it should be taken as soon as possible, but no later than 12 hours. In the event that more than 12 hours have elapsed, the patient should be advised to continue with the next dose at the usual time, without taking the missed tablet.
In the event of missing dose the likelihood of breakthrough bleeding or spotting may be increased.

Paediatric population

There is no relevant use of dydrogesterone before the menarche. The safety and efficacy of dydrogesterone in adolescents aged 12 to 18 years has not been established.

Method of administration
For oral use.
For administration of higher dosages, the tablets must be taken evenly throughout the day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Vaginal bleeding of undetermined cause.
- Presence of severe hepatic disease, or a history of severe hepatic disease, until liver function values have returned to normal.Contraindications for the use of oestrogens in combination with progestogens, such as dydrogesterone, in combined therapy.
- Known or suspected sex hormone-dependent malignancies.
- Meningioma or history of meningioma.

4.4 Special warnings and precautions for use

Before starting treatment with dydrogesterone due to dysfunctional uterine bleeding, an organic cause must be excluded.

Breakthrough bleeding and minor blood loss may occur during the first months of treatment. If breakthrough bleeding and minor blood loss continue to occur when treatment has already been ongoing for some time, or continue when treatment is discontinued, the cause of this must be established, if necessary, by taking an endometrial biopsy to exclude malignancy of the endometrium.

If any of the following conditions occurs during use for the first time or gets worse, discontinuation of treatment must be considered:
- exceptionally severe headache, migraine or symptoms that may indicate cerebral ischaemia,
- marked increase in blood pressure,
- occurrence of venous thromboembolism.

In cases of threatened or habitual miscarriage, viability of the fetus should be ascertained and, during treatment, it should be checked whether the pregnancy is still progressing and/or the embryo is still alive.

The use of dydrogesterone as support of the luteal phase during an ART (Assisted Reproductive Technology) procedure should be discontinued in the event of an abortion or miscarriage.

Conditions for which monitoring is necessary:
The following rare disorders are known to be potentially influenced by sex hormones and may develop or worsen during pregnancy or during the use of sex hormones: cholestatic jaundice, herpes gestationis, severe pruritus, otosclerosis and porphyria.

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, in particular:

Meningioma
The occurrence of meningiomas (single and multiple) has been reported in association with use of Dydrogesterone.
Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any Dydrogesterone containing treatment must be

stopped (see section 4.3). Tumour shrinkage has been observed after treatment discontinuation.

Patients with a history of depression must be carefully monitored; if major depression recurs, treatment with dydrogesterone must be discontinued.

Other conditions
Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Warnings and precautions with regard to using Dydrogesterone Lotus in the indication "For prevention of endometrial hyperplasia in postmenopause":
See also the warnings in the product information for the oestrogen preparation.

For the treatment of postmenopausal symptoms, hormone replacement therapy (HRT) should only be initiated if these symptoms adversely affect quality of life. In all cases, a careful assessment of the benefits and risks of HRT should be made periodically - at least annually - and treatment should only be continued if the benefits outweigh the risks.

Medical examination/follow-up
Before starting hormone replacement therapy (HRT) or when resuming its use after a break, a complete medical history (including family history) must be taken.
A physical examination (including gynaecological and breast examination) should take place based on medical history, as well as the contraindications and warnings. During treatment, it is recommended that regular check-ups be performed, the frequency and nature of which are adapted individually.
Women must be told about which changes in their breasts they must consult with their physician (see paragraph below "Breast cancer").
Examinations, including imaging such as mammography, should be performed in accordance with current guidelines for screening, taking into account the medical situation of the individual woman.

Endometrial hyperplasia and carcinoma
Long-term use of oestrogens without addition of progestogens increases the risk of endometrial hyperplasia and endometrial carcinoma in women with a uterus. Depending on the duration and oestrogen dose, the risk is 2 to 12 times higher than in women not using oestrogens. After discontinuation of oestrogen treatment, the risk persists for at least a further 10 years. This extra risk can be prevented by combining oestrogen therapy with a progestogen, such as dydrogesterone, for at least 12 days per month/28-day cycle.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting occurs after quite some time of therapy or persists after discontinuation of treatment, further investigation is indicated. This may mean that an endometrial biopsy must be taken in order to rule out malignancy.

Breast cancer
All available data indicate an increased risk of breast cancer when women use a combination of oestrogen and progestogen as HRT, or when they only use oestrogen as HRT. This risk depends on the duration of use.

Combined oestrogen-progestogen treatment:
The Women's Health Initiative Study (WHI, a randomised placebo-controlled study) and a meta-analysis of prospective epidemiological studies consistently indicate an increased risk of breast cancer after 3 (1-4) years of use or more (see section 4.8).

Oestrogen monotherapy:
In the WHI study, no increased risk of breast carcinoma was found in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in the risk of breast carcinoma diagnosis, which is lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

Results from a large meta-analysis show that the extra risk decreases after discontinuation of HRT. The time needed for the extra risk to disappear depends on the duration of HRT use. If HRT has been used for more than 5 years, the extra risk may persist for 10 years or more.

As a result of treatment with HRT, particularly combined oestrogen-progestogen treatment, there is an increase in the density of mammographic images, which may be detrimental to the radiological detection of breast cancer.

Ovarian cancer
Ovarian carcinoma is much rarer than breast carcinoma.
A large meta-analysis of epidemiological studies suggests a slightly increased risk in women using oestrogen monotherapy or combined oestrogen-progestogen HRT, which becomes apparent within five years of use, but which decreases again upon termination of treatment.

Some other studies, including the WHI study, suggest that the use of combination HRT is possibly associated with an equivalent or slightly smaller risk (see section 4.8).

Venous thromboembolisms
HRT is associated with a 1.3- to 3-fold higher risk for the development of venous thromboembolisms, i.e. deep vein thrombosis or pulmonary embolism. The risk of developing these is greater during the first year of HRT than thereafter (see section 4.8).

Patients with known thrombophilia are at greater risk of developing VTE and HRT can increase this risk. HRT is therefore contraindicated in these patients.

General known risk factors for VTE are the use of oestrogens, advancing age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/post-partum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus on the possible role of varicose veins in the onset of VTE.

As with all post-operative patients, consideration must be given to taking precautions to prevent VTE after the procedure. If prolonged immobilisation is to take place after elective surgery, it is recommended that HRT be discontinued 4-6 weeks in advance. Treatment must not be resumed until the woman has been fully remobilised.

Women with no personal history of VTE, but with a first-degree relative with thrombosis at a young age, can be offered screening after its limitations have been clearly discussed (only a few thrombophilic disorders can be identified by screening). If a thrombophilic disorder having led to thrombosis in family members has been identified or if the disorder is severe (e.g. antithrombin, protein S or protein C deficiency or a combination of defects), HRT is contraindicated.

In women already receiving anticoagulation treatment, careful consideration of the benefits and risks of HRT must be made.

If a VTE develops after the start of therapy, administration of the medicinal product should be discontinued. Patients must be informed that they should contact their physician immediately if they experience symptoms that may possibly be the result of a thromboembolism (e.g. painful swelling of a leg, sudden chest pain, shortness of breath).

Coronary heart disease (CHD)
Randomised controlled studies have not shown that women with or without pre-existing CHD, who received HRT with oestrogen in combination with progestogen or with oestrogen alone, were protected against myocardial infarction.

Combined oestrogen-progestogen treatment:
The relative risk of developing CHD is slightly increased during HRT with a combination of oestrogen

and progestogen. Since the baseline absolute risk of developing CHD is highly age-dependent, the number of extra cases of CHD as a result of oestrogen-progestogen use in women approaching menopause is very small, but increases with increasing age.

Ischaemic stroke
Use of combined HRT or oestrogen-only HRT is associated with a 1- to 1.5-fold higher risk of ischaemic stroke. The relative risk does not change with increasing age or time since menopause. However, because the baseline risk of stroke is highly dependent on age, the absolute risk will increase with increasing age.

Excipients
This medicine 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 reveal that the main active metabolite 20α-dihydrodydrogesterone (DHD) and, to a lesser extent, dydrogesterone are primarily metabolised by CYP3A4.

Substances that increase the clearance of progestogens (reduced efficacy due to enzyme induction), for example: barbiturates, phenytoin, carbamazepine, primidone, rifampicin and HIV medication such as ritonavir, nevirapine and efavirenz, and possibly also products containing the herbal remedy St. John's wort (*Hypericum perforatum*).

Clinically, an increase in dydrogesterone clearance may lead to a reduction in its effect and changes in the bleeding pattern.

Substances with variable effects on the clearance of progestogens
Many combinations of HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can, if concomitantly administered with progestogens, raise or lower the plasma concentrations of progestogens. In some cases, the net effect of these changes may be clinically relevant.
Hence, the prescribing information of concomitantly administered HIV/HCV medicines must be consulted to establish potential interactions and any associated recommendations.

Substances that lower the clearance of progestogens (enzyme inhibitors)
The clinical relevance of possible interactions with enzyme inhibitors is unknown. Concomitant use of strong CYP3A4 inhibitors may increase the plasma concentrations of progestogens.

4.6 Fertility, pregnancy and lactation

Pregnancy
It is estimated that over 9 million women have already been exposed to dydrogesterone during pregnancy. To date, there have been no indications that the use of dydrogesterone during pregnancy has a harmful effect. In the literature, a study is described in which it was found that the use of some progestogens may be associated with an increase in the risk of hypospadia occurrence. However, as this has not been clearly confirmed to date in other studies, no definitive conclusion can be made with regard to the effect of progestogens on the occurrence of hypospadia.

Clinical studies where a limited number of women were treated with dydrogesterone during the first stage of pregnancy did not show that the risk is increased. To date, there are no other epidemiological data available.

The effects observed during non-clinical studies into embryofetal and postnatal development were consistent with the pharmacological profile. Undesirable effects only occurred in the event of exposure that was considerably higher than the maximum exposure in humans (see section 5.3).

Dydrogesterone may be administered during pregnancy if there is a clear indication for this.

Breast-feeding
It is unknown whether dydrogesterone is excreted in human milk. No research has been done into the excretion of dydrogesterone in human milk. Experience with other progestogens indicate that progestogens and their metabolites are found in small quantities in human milk. It is not known whether there is a risk for the infant. Dydrogesterone must therefore not be used during breast-feeding.

Fertility
There are no data on the effect of dydrogesterone on fertility.

4.7 Effects on ability to drive and use machines

Dydrogesterone has minor influence on the ability to drive and use machines.

In rare cases, dydrogesterone may cause slight somnolence and/or dizziness, particularly during the first couple of hours post-dose. Caution must therefore be exercised when driving and using machines.

4.8 Undesirable effects

The most commonly reported adverse reactions of this product in patients treated with dydrogesterone during clinical studies in the indications without oestrogen use were vaginal bleeding, metrorrhagia, breast pain/tenderness, nausea, vomiting, abdominal pain and migraine/headache.

The following adverse reactions, at the frequencies stated, have been observed during clinical studies with dydrogesterone (n=3 483) in indications without oestrogen use, in two company-sponsored, interventional clinical studies for luteal phase support as part of assisted reproductive technologies (ART) with dydrogesterone (n=1 036), and have been reported spontaneously. Frequencies are based on the most conservative approximation.

Organ class according to MedDRA database	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1 000 to <1/100**	**Rare ≥1/10 000 to <1/1 000**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				Growth of progestogen-dependent neoplasms (e.g. meningioma)*
Blood and lymphatic system disorders				Haemolytic anaemia*
Psychiatric disorders			Depressed mood	
Immune system disorders				Hypersensitivity
Nervous system disorders		Migraine/ headache	Dizziness	Somnolence
Gastrointestinal disorders		Nausea Vomiting Abdominal pain		
Hepatobiliary disorders			Impaired hepatic function (with jaundice, asthenia or malaise, and abdominal pain)	

Skin and subcutaneous tissue disorders			Allergic dermatitis (e.g. rash, pruritus, urticaria)	Angioedema*
Reproductive system and breast disorders	Vaginal bleeding	Impaired menstruation (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Breast pain/tenderness		Swelling of the breasts
General disorders and administration site conditions				Oedema
Investigations			Weight gain	

* Adverse reactions reported spontaneously but not observed during clinical studies have been classified as "rare", given the fact that the upper limit of the 95% confidence interval for the estimated frequency is no higher than 3/x, where x=3 483 (the total number of patients in the clinical studies).

Adverse reactions that may occur during oestrogen-progestogen treatment (see also section 4.4 and the product information for the oestrogen preparation):

- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Ovarian carcinoma:
  Use of oestrogen monotherapy or combined oestrogen-progestogen HRT is associated with a slightly increased risk of ovarian carcinoma diagnosis (see section 4.4). A meta-analysis of 52 epidemiological studies revealed an increased risk of ovarian carcinoma in women using HRT, compared to women who have never used HRT (RR 1.43; 95% CI 1.31-1.56). For women aged 50 to 54 years using HRT for five years, this leads to approximately 1 extra case per 2 000 users. Among women aged 50 to 54 years not using HRT, about 2 women per 2 000 will be diagnosed with ovarian carcinoma over a period of 5 years.
- Venous thromboembolism
- Myocardial infarction, coronary heart 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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Dydrogesterone is a substance with very low toxicity. Nausea, vomiting, drowsiness and dizziness are symptoms that can theoretically occur in case of overdose. There are no known cases where overdose with dydrogesterone has resulted in harmful sequelae.

Treatment

Specific treatment is apparently not necessary. Symptomatic treatment can be considered in the event of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: genitourinary system and sex hormones, ATC code: G03DB01.

Mechanism of action
Dydrogesterone is a synthetic progestogen with an oral bioavailability that causes a secretory phase of the endometrium in a uterus prepared by oestrogen. It gives protection against the increased risk of endometrial hyperplasia and/or endometrial carcinoma induced by oestrogens. Dydrogesterone has no oestrogenic, androgenic, anabolic and corticoid activity.

Dydrogesterone does not suppress ovulation. As a result, conception remains possible when dydrogesterone is used by women of childbearing age.

In postmenopausal women with a uterus, oestrogen replacement leads to an increase in the risk of endometrial hyperplasia and endometrial carcinoma. Addition of a progestogen prevents this extra risk.

Clinical efficacy and safety
Support of the luteal phase during an ART (Assisted Reproductive Technology) procedure:

A randomised, double-blind, double-dummy, multicentre, comparative study was conducted comparing the efficacy, safety and tolerability of 30 mg daily orally administered dydrogesterone with 600 mg daily intravaginally administered micronised progesterone for luteal support during in vitro fertilisation (IVF) treatment (LOTUS I).

A randomised, open-label, multicentre, comparative study was conducted comparing the efficacy, safety, and tolerability of 30 mg daily orally administered dydrogesterone with 90 mg daily intravaginally administered progesterone gel Crinone 8% for luteal support during in vitro fertilisation (IVF) treatment (LOTUS II).

These studies demonstrated non-inferiority of treatment with orally administered dydrogesterone in comparison with intravaginally administered micronised progesterone, as guided by the presence of fetal heartbeat at 12 weeks of pregnancy (gestational week 10).

In the investigated study population, pregnancy rates of 37.6% and 33.1% (LOTUS I) versus 36.7% and 34.7% (LOTUS II) were measured at 12 weeks of pregnancy (gestational week 10). The difference in pregnancy rate between both groups was 4.7 (95% CI, -1.2; 10.6) in LOTUS I and 2.0 (95% CI, -4.0; 8.0) in LOTUS II.

Within the safety sample of 1 029 women (LOTUS I) and 1 030 women where at least one dose of study medication was administered, the incidence of treatment-emergent adverse events (TEAEs) was similar between both treatment groups.

Due to the nature of the indication and the investigated study population, a number of early abortions and miscarriages can be expected. Especially up to a pregnancy of 12 weeks (gestational week 10), the expected pregnancy rate is about 35%.

The safety profile as observed in both LOTUS studies is consistent with the profile known for dydrogesterone for the treatment target group and indication.

5.2 Pharmacokinetic properties

Absorption
After oral administration of dydrogesterone 10 mg tablet, dydrogesterone is rapidly absorbed. Peak plasma concentrations are approximately 3.2 ng/mL and 57 ng/mL for dydrogesterone and active metabolite 20α-dihydrodydrogesterone (DHD), respectively; the corresponding median t_{max} values are 0.75 and 1.75 h, respectively. Absolute bioavailability (AUC) is approximately 9.1 and 220 ng.h/mL for dydrogesterone and DHD, respectively.

Absolute bioavailability of dydrogesterone (20 mg oral dose versus 7.8 mg intravenous infusion) is 28%.

After a single dose, food intake may delay the peak plasma concentration of dydrogesterone by approximately 1 hour, resulting in an approximately 20% lower peak plasma concentration of dydrogesterone without affecting the degree of dydrogesterone and DHD exposure.

The observed effect of concomitant food intake on the peak plasma concentration is not regarded as clinically relevant. Therefore, dydrogesterone 10 mg tablet can be taken at the same time as food.

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
After oral administration, dydrogesterone is rapidly metabolised to DHD. *In vitro* data show that the major metabolic pathway generating DHD is catalysed in human cytosol by aldo-keto reductase 1C (AKR 1C). In addition to this cytosolic metabolism, there are metabolic conversions by cytochrome P450 isoenzymes (CYPs), almost exclusively via CYP3A4, forming several less important metabolites. Levels of the major active metabolite DHD show a peak at the same time as dydrogesterone after administration. The plasma levels of DHD are substantially higher than the parent drug. The AUC and C_{max} ratios of DHD and dydrogesterone are 25 and 20, respectively. The mean terminal half-life of both dydrogesterone and DHD is approximately 15 hours. A common feature of all metabolites characterised is the retention of the parent compound's 4,6-diene-3-one configuration and the absence of 17α-hydroxylation. This explains the absence of oestrogenic and androgenic effects of dydrogesterone.

Elimination
After oral administration of labelled dydrogesterone, an average of 63% of the dose is excreted in the urine. Total plasma clearance is 6.4 L/minute. Excretion is complete within 72 hours. DHD is mainly present in the urine as the conjugated glucuronic acid.

Dose/time dependency
Single- and multiple-dose pharmacokinetics are linear over the oral dose range of 2.5 to 20 mg. Comparison of single- and multiple-dose kinetics shows that the pharmacokinetics of dydrogesterone and DHD are not altered as a result of repeated dosing. Steady state is generally reached after 3 days of treatment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.
Studies into the toxic effects on reproduction in rats show an increased incidence of prominent nipples (between days 11-19 of the lactation period) and hypospadias in male rats at high doses (> 80 times the human exposure). The clinical relevance of these observations is not known.

The limited safety data in animals indicate that dydrogesterone has a prolonging effect on labour, which is consistent with the progestogenic action.

Environmental Risk Assessment (ERA)
Environmental risk assessment studies have shown that Dydrogesterone may pose a risk for aquatic compartment. Medicinal products no longer used must not be disposed of via household waste or waste water. Any unused medicinal product or waste material should be disposed of in accordance with local requirements or returned to the pharmacy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet composition:
Lactose monohydrate
Maize starch pregelatinized
Hypromellose 2910 E464
Silica, colloidal anhydrous
Magnesium stearate E572

Composition of the coating:
Lactose monohydrate
Hypromellose E464
Titanium dioxide E171
Triacetin E1518

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

The tablets are packed in PVC/PVDC-Alu blisters.
Dydrogesterone Lotus is available in boxes containing 10, 14, 20, 30 or 42 tablets per box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment. (See section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Lotus Pharma Bulgaria EOOD
Cherni Vrah No 102d
Floor 4 Triaditsa District
1407 Sofia
Bulgarije

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 131665

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 17 december 2024

10. DATE OF REVISION OF THE TEXT