SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LUTINUS 100 mg vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vaginal tablet contains 100 mg progesterone.

Excipient with known effect: 1 vaginal tablet contains approximately 760 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal tablet
White to off-white convex and oblong tablets debossed with “FPI” on one side and “100” on the other side.

The vaginal tablets are supplied with one polyethylene vaginal applicator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUTINUS is indicated for luteal support as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.

4.2 Posology and method of administration

Posology

Adults
The dose of LUTINUS® is 100 mg administered vaginally three times daily starting at oocyte retrieval. The administration of LUTINUS should be continued for 30 days, if pregnancy has been confirmed.

Paediatric population
There is no relevant use of LUTINUS in the paediatric population.

Elderly

No clinical data have been collected in patients over age 65.

Use in special populations
There is no experience with use of LUTINUS in patients with impaired liver or renal function.

Method of administration
LUTINUS is to be placed directly into the vagina by the applicator provided.

4.3 Contraindications

LUTINUS should not be used in individuals with any of the following conditions:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Undiagnosed vaginal bleeding
- Known missed abortion or ectopic pregnancy
- Severe hepatic dysfunction or disease
- Known or suspected breast or genital tract cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events
- Porphyria

4.4 Special warnings and special precautions for use

LUTINUS should be discontinued if any of the following conditions are suspected: myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis.

Cautious use in patients with mild to moderate hepatic dysfunction.

Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.

Because progesterone may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
A decrease in insulin sensitivity and thereby in glucose tolerance has been observed in a small number of patients on oestrogen-progestogen combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progesterone therapy.

Sex steroid use may also increase the risk of retinal vascular lesions. To prevent these latter complications, caution is to be taken in users >35 years, in smokers, and in those with risk factors for atherosclerosis. Use should be terminated in case of transient ischemic events, appearance of sudden severe headaches, or vision impairments related to papillary edema or retinal hemorrhage.

Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.

Before starting treatment with LUTINUS, the patient and her partner should be assessed by a doctor for causes of infertility.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine or St. John's wort (*Hypericum perforatum*)-containing herbal products) may increase the elimination rate and thereby decrease the bioavailability of progesterone.
In contrast ketoconazole and other inhibitors of cytochrome P450-3A4 may decrease elimination rate and thereby increase the bioavailability of progesterone.
The effect of concomitant vaginal products on the exposure of progesterone from LUTINUS has not been assessed. However, LUTINUS is not recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal tablet.

4.6 Fertility, pregnancy and lactation

Pregnancy:
LUTINUS vaginal tablets are only indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) regimen.

There is yet limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy.

In the pivotal trial, the rate of foetal anomalies following 10-week exposure to LUTINUS 100 mg TID was 4.5% in the LUTINUS TID group, a total of 7 cases of foetal anomalies (i.e. oesophageal fistula, underdeveloped right ear with hypospadias, small aorta/ valvular regurgitation/ deviated septum, hand deformity, cleft palate/cleft lip, hydrocephalus and holoprosencephaly/ proboscis/ polydactylia) were seen in 404 patients. The rate of foetal anomalies observed during the clinical trial is comparable with the event rate described in the general population, although the total exposure is too low to allow conclusions to be drawn.

During the conduct of the pivotal clinical trial, the number of spontaneous abortions and ectopic pregnancies associated with the use of LUTINUS 100 mg TID were 5.4% and 1%, respectively.

Lactation:
Detectable amounts of progesterone have been identified in the milk of mothers. Therefore LUTINUS should not be used during lactation.

4.7 Effects on ability to drive and use machines

LUTINUS has minor or moderate influence on the ability to drive and use machines. Progesterone may cause drowsiness and/or dizziness; therefore caution is advised in drivers and users of machines.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with LUTINUS in IVF patients during clinical trials are headache, vulvovaginal disorders and uterine spasm, reported in 1.5%, 1.5% and 1.4% subjects, respectively. The table below displays the main adverse drug reactions in women treated with LUTINUS in the clinical trial distributed by system organ classes (SOCs) and frequency.

System Organ Class (SOC)	**Common (> 1/100 and < 1/10)**	**Uncommon (> 1/1000 and <**	**Not known*** (cannot be**

		1/100)	estimated from the available data)
Nervous system disorders	Headache	Dizziness, Insomnia	Fatigue
Gastrointestinal disorders	Abdominal distension Abdominal pain Nausea	Diarrhoea Constipation	Vomiting
Skin and subcutaneous tissue disorders		Urticaria Rash	Hypersensitivity reactions
Reproductive system and breast disorders	Uterine spasm	Vulvovaginal disorders* Vaginal mycosis Breast disorders** Pruritus genital	
General disorders and administration site conditions		Oedema peripheral	

* Vulvovaginal disorders such as vulvovaginal discomfort, vaginal burning sensation, vaginal discharge, vulvovaginal dryness and vaginal haemorrhage, have been reported following use of LUTINUS, with cumulative reporting frequency of 1.5%.

** Breast disorders, such as breast pain, breast swelling and breast tenderness have been reported in the clinical trial as single cases, with cumulative reporting frequency of 0.4%.

***Cases seen during post marketing experience.

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 to:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

4.9 Overdose
High doses of progesterone may cause drowsiness.

Treatment of overdosage consists of discontinuation of LUTINUS together with institution of appropriate symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives

ATC code: G03DA04.

Mechanism of action
Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

Clinical efficacy and safety
Ongoing pregnancy and live birth rates following 10-week luteal support with LUTINUS 100 mg TID (N=390) in patients who had an embryo transfer in the Phase III clinical trial were 44% (95% CI 38.9; 48.9) and with 39.5% (95% CI 34.6; 44.5), respectively

5.2 Pharmacokinetic properties

Absorption
Progesterone serum concentrations increased following the administration of the LUTINUS vaginal tablets in 12 healthy premenopausal females. On day 1 of treatment, the mean C_{max} 19.8 ± 2.9 ng/mL with a T_{max} of 17.3 ± 3.0 hours after administration of LUTINUS three times daily 8 hours apart.

On multiple dosing, steady state concentrations were attained within approximately 1 day after initiation of treatment with LUTINUS. Trough values of 10.9 ± 2.7 ng/mL were observed with an AUC_{0-24} of 436 ± 43 ng*hr/mL on Day 5.

Distribution
Progesterone is approximately 96 % to 99 % bound to serum proteins, primarily to serum albumin and corticosteroid binding globulin.

Biotransformation
Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Elimination
Progesterone undergoes renal and biliary elimination.
Following injection of labelled progesterone, 50-60% of the excretion of metabolites occurs via the kidney; approximately 10% occurs via the bile and faeces. Overall recovery of the labelled material accounts for 70% of an administered dose. Only a small portion of unchanged progesterone is excreted in the bile.

5.3 Preclinical safety data

Progesterone is a well known natural reproductive steroidal hormone in humans and animals, with no known toxicological effects. Therefore no toxicity studies have been performed with this progesterone vaginal dosage form, with the exception of local tolerance and skin sensitization studies.

LUTINUS was found to be non-irritative for up to 90 days of twice daily vaginal administration in rabbits, and was also shown to be non-sensitising in Guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, hydrophobic colloidal
Lactose monohydrate
Pregelatiniszed maize starch
Povidone
Adipic acid
Sodium hydrogen carbonate
Sodium laurilsulfate
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original container in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Alu/Alu blisters of 3 vaginal tablets.

The blisters are available in cartons packed:
21 or 90 vaginal tablets with 1 vaginal applicator respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

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Fabrikstraße 7
D-24103 Kiel
Tel.: +49-(0)431-58 52 - 0
Fax: +49-(0)431-58 52 - 74

8. MARKETING AUTHORISATION NUMBER(S)

06336/06966/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jul 25, 2021

10. DATE OF REVISION OF THE TEXT

October 2015

11. PRESCRIPTION/PHARMACY STATUS

Prescription only

For further information please feel free to contact us at the following e-mail address: info-service@ferring.de