Version 4, 02/2016

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT 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 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 Lutinus100 mg TID were 5.4% and 1%, respectively.

Breast-feeding
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 < 1/100)**	**Not known*** ** (cannot be 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 via <the national reporting system> <[to be completed nationally]>

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 Cmax 19.8 ± 2.9 ng/mL with a Tmax 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 AUC0-24 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 K29/32
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 with 21 or 90 vaginal tablets with 1 vaginal applicator.
Not all pack sizes may be marketed.

<[To be completed nationally]>

6.6 Special precautions for disposal <and other handling>
No special requirements.

1. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2009-11-19

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING (CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Lutinus
100 mg vaginal tablets
progesterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vaginal tablet contains 100 mg progesterone

3. LIST OF EXCIPIENTS

Hydrophobic colloidal silica, lactose monohydrate, pregelatinised maize starch, povidone, adipic acid, sodium hydrogen carbonate, sodium laurilsulfate and magnesium stearate

4. PHARMACEUTICAL FORM AND CONTENTS

21 vaginal tablets with 1 vaginal applicator.
90 vaginal tablets with 1 vaginal applicator.
<[To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR VAGINAL USE ONLY
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring <{locally company (Marketing Authorisation Holder) }>

<{to be completed nationally}>

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUTINUS

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS
aluminium/aluminium peel blisters (3 x 1 vaginal tablet)

1. NAME OF THE MEDICINAL PRODUCT

Lutinus
100 mg vaginal tablets
progesterone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ferring {local company}
{to be completed nationally}

3. EXPIRY DATE

EXP XX/XX

4. BATCH NUMBER

Lot XXXX.XXX

5. OTHER

[ARROW]
FOR VAGINAL USE ONLY

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{(Invented) name strength pharmaceutical form}

<{(Invented) name and associated names (see Annex I) strength pharmaceutical form}>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Active substance(s)}
{Route of administration}

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

<[To be completed nationally]> *[For referral procedures, as appropriate]*

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Lutinus 100 mg vaginal tablets
progesterone

Read all of this leaflet carefully before you start using 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. See section 4.

What is in this leaflet:

1. What Lutinus is and what it is used for

This medicine is provided as a vaginal tablet that contains the natural female sex hormone progesterone.

Lutinus is for women who need extra progesterone while undergoing treatment in an Assisted Reproductive Technology (ART) programme.

Progesterone acts on the lining of the womb and it helps you to become and to stay pregnant when you are treated for infertility.

2. What you need to know before you use Lutinus

Lutinus can be used only in women who are undergoing infertility treatment in an Assisted Reproductive Technology (ART) programme. The treatment is started on the day of egg retrieval. Your doctor will tell you when the treatment is started.

Do not use Lutinus
- if you are allergic to progesterone or any of the other ingredients of this medicine (listed in section 6).
- if you have unusual vaginal bleeding that has not been evaluated by the doctor.
- if you have a miscarriage and your physician suspects some tissue is still in the uterus or pregnancy outside of the womb.
- if you currently have or have had severe liver problems.
- if you have known or suspected breast or genital tract cancer.
- if you have or have had blood clots in the legs, lungs, eyes or elsewhere in the body.
- if you have porphyria disorders (a group of inherited or acquired disorders of certain enzymes).

Warnings and precautions
Take special care and tell your doctor straight away if you experience any of these symptoms during treatment or even few days after the last dosage:

- pains in the calves or chest, a sudden shortness of breath or coughing blood indicating possible clots in the legs, heart, or lungs
- severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg indicating possible clots in the brain or eye
- worsening symptoms of depression

Before treatment with Lutinus tell your doctor if you have had or have any of the following health problems:
- Epilepsy
- Migraine
- Asthma
- Cardiac or renal dysfunction
- Diabetes

Children
There is no relevant use of Lutinus in children.

Other medicines and Lutinus
Tell your doctor if you are using, have recently used or might use any other medicines.

Some medicines may interact with vaginal progesterone tablets. For example, carbamazepine, rifampin as well as St. John's wort-containing herbal products may decrease the effectiveness, whereas products containing ketoconazole and vaginal antifungal creams may alter the actions of progesterone.

Pregnancy and breast-feeding
Lutinus can be used during the first trimester of pregnancy for women who need extra progesterone while undergoing treatment in an Assisted Reproductive Technology (ART) programme.

The risks of congenital (conditions present at birth) anomalies, including genital abnormalities in male or female infants, from exposure to exogenous progesterone during pregnancy have not been fully established.

This medicine should not be used during breast feeding.

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

3. How to use Lutinus

Always use this medicine exactly as your doctor has told you. You should check with your doctor if you are not sure.

The usual dose is 100 mg placed directly into your vagina three times daily starting on the day of egg retrieval. The administration of Lutinus should be continued for 30 days if pregnancy has been confirmed.

Instructions for use
Lutinus is to be placed directly into your vagina by using the applicator provided.

1. Remove one blister from the strip by tearing along the perforations.

2. To remove the foil seal on the back of the blister, start in the corner of the blister pack that has a printed arrow

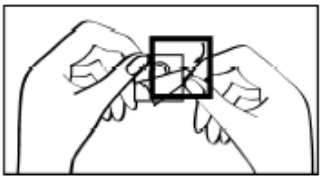
3. Unwrap the applicator.

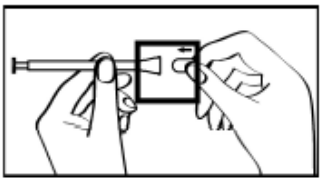
4. Put one tablet in the space provided at the end of the applicator. The tablet should fit securely and not fall out.

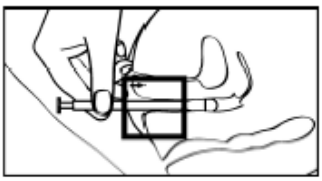
5. The applicator with the tablet may be inserted into the vagina while you are standing, sitting, or when lying on your back with your knees bent. Gently insert the thin end of the applicator well into the vagina.

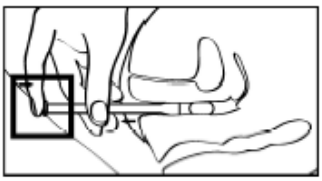
6. Push the plunger to release the tablet.

Remove the applicator and rinse it thoroughly in warm running water, wipe dry with a soft tissue and keep the applicator for subsequent use.









If you use more Lutinus than you should
Please consult your doctor or pharmacist if you have used more Lutinus than your doctor has told you.

If you forget to use Lutinus
Take the dose as soon as you remember and then carry on as before. Do not take a double dose to make up for a forgotten dose.

If you stop using Lutinus
Please consult your doctor or pharmacist for advice if you intend to stop or have stopped using Lutinus. Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.

4. Possible side effects

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

The most common side effects are headache, vaginal disorders and uterine cramping.

The following common side effects affect between 1 and 10 of every 100 patients treated:
- Headache
- Abdominal distension (swelling in the abdomen)
- Abdominal pain
- Nausea
- Uterine cramping

The following uncommon side effects affect between 1 and 10 of every 1000 patients treated:
- Dizziness
- Insomnia
- Diarrhoea
- Constipation
- Urticaria (allergic rash)
- Rash
- Vaginal disorders (e.g. vaginal discomfort, burning sensation, discharge, dryness, and bleeding)
- Fungal infection in vagina
- Breast disorders (e.g. breast pain, breast swelling and breast tenderness)
- Itching in the genital area
- Peripheral edema (swelling due to the build up of fluid)

The following side effects have been seen after the product was marketed. Frequency is not known (cannot be estimated from the available data):
- Fatigue
- Vomiting
- Allergic reactions

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via <the national reporting system> <[to be completed nationally]> By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lutinus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in the original container in order to protect from light.

This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lutinus contains

The active substance is progesterone.

Each vaginal tablet contains 100 mg progesterone.

The other ingredients are:
- Hydrophobic colloidal silica
- Lactose monohydrate
- Pregelatinised maize starch
- Povidone
- Adipic acid
- Sodium hydrogen carbonate
- Sodium laurilsulfate
- Magnesium stearate

What Lutinus looks like and contents of the pack
This medicine is a vaginal tablet. It is a white to off-white convex and oblong tablets debossed with "FPI" on one side and "100" on the other side.

Pack sizes: 21 or 90 vaginal tablets, supplied with one polyethylene vaginal applicator. Not all pack sizes may be marketed.

<[To be completed nationally]>

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Ferring {local company}
{To be completed nationally}

Manufacturer
Ferring GmbH
Wittland 11, D-24109 Kiel, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:
Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Iceland, Ireland, the Netherlands, Norway, Poland, Slovak Republic, Spain and Sweden: Lutinus
Portugal: Luferti
Romania: Lutinus 100 mg, comprimate vaginale
Slovenia: Lutinus 100 mg vaginalne tablete
United Kingdom: Lutigest

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}.>

<[To be completed nationally]>