PRODUCT MONOGRAPH

Pr Utrogestan®

Progesterone vaginal capsule

200 mg

Progestin

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PrUTROGESTAN®

Progesterone vaginal capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Vaginal	capsule / 200 mg	Gelatin, Soya lecithin. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

UTROGESTAN (progesterone) is indicated for luteal phase support during *in vitro* fertilization (IVF) cycles.

Pediatrics*:* This drug is not intended for pediatric use and no clinical data have been collected in children.

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

CONTRAINDICATIONS

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

- Hypersensitive to progesterone, soya lecithin, gelatin or to any other ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph
- Known missed abortion or ectopic pregnancy
- Severe hepatic dysfunction or disease
- Known or suspected breast cancer or genital tract cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis or cerebro-vascular disease, or a history of these events.

- Porphyria
- Undiagnosed Vaginal Bleeding

WARNINGS AND PRECAUTIONS

General

- Before starting treatment, the patient and her partner should be assessed by a doctor for causes of infertility.
- A pretreatment physical examination should include special reference to breasts, pelvic organs as well as Papanicolaou smear.
- In all cases of irregular vaginal bleeding adequate diagnostic measures should be undertaken.
- Progesterone may cause fluid retention and conditions which might be influenced by this (e.g., epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation (e.g., epilepsy, migraine, asthma, cardiac or renal dysfunction).
- The pathologist should be informed of progesterone therapy when relevant specimens are submitted.
- Endometrin UTROGESTAN should not be recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal insert [see Drug Interactions].
- 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
- UTROGESTAN (progesterone) is not suitable for use as a contraceptive and is not a treatment for premature labour.

Cardiovascular

The physician should be alert to earliest signs of myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis or retinal thrombosis. UTROGESTAN should be discontinued if any of these are suspected.

Hepatic/Biliary/Pancreatic

Cautious use in patients with mild to moderate hepatic dysfunction.

Metabolic

Decrease in glucose tolerance has been noted in a few patients when taking oestrogen- progestin combination drugs. The mechanism for this is unknown. Diabetic patients should be carefully monitored while receiving progesterone therapy.

Psychiatric

Patients who have a history of depression should be carefully observed. UTROGESTAN should be discontinued if symptoms worsen.

Special Populations

Pregnancy
During pregnancy, UTROGESTAN® should only be used during the first three months. UTROGESTAN® is not a treatment for premature labour. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Progesterone crosses the placenta. No association has been found between the maternal use of progesterone in early pregnancy and fetal malformations. Data on the risk of fetal effects with exposure in later stages of pregnancy are limited.

Nursing Mothers
Detectable amounts of progesterone have been identified in the milk of mothers receiving oral progestins. The effect of this on the nursing infant has not been determined. UTROGESTAN should not be used during lactation

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Local intolerance (burning, pruritus or fatty discharge) has been observed during the different

clinical trials and reported in the literature. Most local adverse events are mild in nature.

No systemic side effects, in particular somnolence or dizziness (observed with the oral form) have been reported during clinical studies at the recommended dosages.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

A randomized, controlled, open label, comparative clinical trial enrolled 430 women undergoing IVF that were treated with either UTROGESTAN 200 mg three times daily (n=218) or Progesterone gel 8% twice daily (n=212) from embryo transfer until 12 weeks of pregnancy. 1 patient (0.5%) in the UTROGESTAN group discontinued the trial because of an adverse event (suspicious cervical smear) and 1 patient discontinued the trial because of local intolerance (0.5%). In the Progesterone gel 8% group, overall 5 patients discontinued, due to local intolerance (3/5), severe itching (1/5) and ovarian hyperstimulation syndrome (1/5).

Overall, 21 patients (9.7 %) in the UTROGESTAN group and 21 patients (9.9 %) in progesterone gel group reported adverse events.

Adverse events occurring at a frequency of ≥ 1% in the clinical trial are presented in Table 1.

Table 1 - Adverse Events That Occurred in ≥ 1% Of Patients, In Both Treatment[1] Groups, In A Randomized, Controlled, Open Label, Comparative Clinical Trial

	UTROGESTAN n= 218 (%)	**Progesterone gel 8% n= 212 (%)**
Digestive		
Nausea or emesis	1	0
Genitourinary		
Ovarian hyperstimulation syndrome	3	4
Sexual Function/Reproduction		
Vaginal spotting or bleeding	1	1
Vaginal discharge	0	3
Skin		
Local irritation	0	2

[1] Vaginal administration of each treatment: from evening of embryo transfer until 12th week of pregnancy

Local tolerability was additionally assessed, based on patient interview and gynecological examination at 4, 8, and 12 weeks of pregnancy. In the UTROGESTAN group, there were a total of 28 local reactions reported (erythema (14), burning (6), vaginal discharge (5) and itching (3)) in 15 patients (6.9 %). In the 8% progesterone gel group, there were a total of 31 local reactions (erythema (16), burning (6), vaginal discharge (2) and itching (7)) in 15 patients (7.1 %). Local reactions in both groups were mild in the majority of cases.

In a clinical study in which 24 healthy subjects received a single 200 mg vaginal administration of UTROGESTAN, the most common adverse events reported were tiredness (54%), headache (17%) and nausea (12.5%).

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of Utrogestan administered vaginally. Because the adverse experiences are reported voluntarily from a population of uncertain size, it is not possible to estimate reliably their frequency or establish a definite causal relationship to drug exposure.

Gastrointestinal disorders: nausea

Nervous system disorders: dizziness

Reproductive system and breast disorders: Administration site reactions

Immune system disorders: Hypersensitivity reactions

Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted for UTROGESTAN. Drugs known to induce the hepatic cytochrome-P450-3A4 system (such as rifampicin, carbamazepine) may increase the elimination of progesterone.

UTROGESTAN may interfere with the effects of bromocriptine and may raise the plasma concentration of cyclosporin.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50} <0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

The effect of concomitant vaginal products on the exposure of progesterone from Utrogestan has not been assessed. Utrogestan is not recommended for use with other vaginal products (such as

antifungal products) as this may alter progesterone release and absorption from the vaginal insert.

Drug-Laboratory Test Interactions

UTROGESTAN may affect the results of laboratory tests of hepatic and/or endocrine functions. The pathologist should be informed of progesterone therapy when relevant specimens are submitted.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dosage is 600 mg/day in divided doses, from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.

Missed Dose
If a patient misses a dose, the patient should be instructed to take the dose as soon as she remembers. The patient should also be instructed not to use more than her daily dose and not to double dose.

Administration
The method of administration is vaginal. Each capsule of UTROGESTAN must be inserted deep into the vagina.

OVERDOSAGE

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Progesterone is a naturally occurring steroid that is secreted by the ovary (corpus luteum), placenta, and adrenal gland. Progesterone exerts its action primarily on the uterus. 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 a pregnancy.

Pharmacokinetics

Absorption:

A randomized, crossover study compared the plasma bioavailability of progesterone after single dose vaginal administration of 200 mg UTROGESTAN vaginal capsule and 1.125 g of a 8% progesterone gel (containing 90 mg of progesterone). Healthy non-pregnant women (aged 19-38 years) received both treatments between Day 4 and 18 of the menstrual cycle on were on an oral estradiol analogue/progestin combination contraceptive to ensure suppression of endogenous progesterone secretion. The main pharmacokinetic results for UTROGESTAN are presented below (the AUC and Cmax were calculated after adjustment to endogenous progesterone):

Mean (±SD) Plasma Pharmacokinetic Parameters for Progesterone Following Single dose Vaginal Administration of Utrogestan 200mg Capsule or 1.125 g of Progesterone Gel 8%

Parameter	Utrogestan	Progesterone 8% Gel	Ratio or *Difference (90% Confidence Intervals)
$C_{\delta max}$ (ng/mL)	6.87 ± 1.80	6.83 ± 2.32	103.4% (92.4-115.8%)
T_{max} (h)	40.55 ± 29.10	10.08 ± 6.11	28.73 (17.01-38.88)
AUC_{δ} (ng·h/mL)	281.9 ± 120.8	189.4 ± 96.9	146.1% (126.2-169.1%)
$T_{1/2}$ (h)	14.82 ± 10.00	17.47 ± 9.13	88.2% (67.0-116.3)

N = 23; ¥ AUC_{δ} until the last concentration above the limit of quantification
AUC_{δ} = Area under the net plasma concentration—time curve; $C_{\delta max}$ = maximum plasma concentration increase
$T_{1/2}$ = Apparent terminal half-life; T_{max} = Time to maximum plasma concentration.

The maximum plasma concentration increase above baseline (Cδmax) and terminal half-life of plasma progesterone were comparable following both treatments. Systemic availability was almost 50% greater with Utrogestan compared with the progesterone gel and the Tmax was 29 hours later with Utrogestan.

On multiple vaginal dosing of Utrogestan 200 mg three times daily, a steady-state progesterone concentration of 11.63 ng/mL ± 3.55 (mean ± SD) was achieved.

Distribution:

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

Metabolism:

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.

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

STORAGE AND STABILITY

Store UTROGESTAN between 15- 30°C. Do not refrigerate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

UTROGESTAN is supplied in blister packages, with 7 capsules per blister package. Each box contains 3 blisters, corresponding to 21 capsules per box.

UTROGESTAN 200 mg soft capsules are ovoid, slightly yellow soft gelatin capsules.

Medicinal ingredient: each capsule contains 200 mg micronized progesterone.
Non-medicinal ingredients: gelatin, glycerol, soybean lecithin, sunflower oil, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

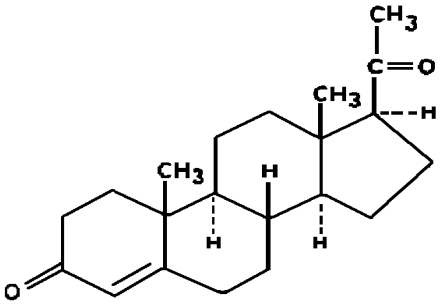
Proper name: Progesterone

Chemical name: Pregn-4-ene-3,20-dione

Molecular formula: $C_{21}H_{30}O_2$

Molecular mass: 314.47

Structural formula:



Physicochemical properties:

Micronized progesterone is a white or almost white crystalline powder or colourless crystals. The form used Utrogestan is the alpha-crystalline form, and has a melting point of 126°C - 131°C.

Progesterone is practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

CLINICAL TRIALS

Study demographics and trial design

Study #1 compared the efficacy and tolerability of UTROGESTAN and Progesterone gel 8% in women undergoing a first IVF or intracytoplasmic sperm injection cycle after successful transfer of two or three embryos.

Table 2 - Summary of patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (Range)	Gender
1	multicentre, randomized, controlled, open-label, parallel-group	UTROGESTAN 600 mg daily (200 mg t.i.d.., vaginal administration, from evening of embryo transfer until 12th week of pregnancy	N = 218	30.7± 2.9 (22-35)	female
		1.125 g Progesterone gel 8% b.i.d. vaginal administration, from evening of embryo transfer until 12th week of pregnancy	N = 212	30.1± 3.0 (23-35)	

Treatment groups were comparable with respect to demographic data and other baseline conditions. A high rate of compliance with the drug treatment was observed in both the UTROGESTAN (98%) and the progesterone gel (8% w/v) (94%) groups. Demographic data for the women randomized to each of the two treatment groups, UTROGESTAN (N= 218) Progesterone gel 8% (N= 212), are shown in Table 3.

Table 3: Demographic data, infertility, and ART-specific characteristics of patients

Variable	UTROGESTAN group N (%)	Progesterone gel 8% N (%)
Randomized patients (n)	218	212
Cause of infertility		
Tubal factor	66 (30.3)	48 (22.6)
Male factor	104 (47.7)	117 (55.2)
Endometriosis	12 (5.5)	16 (7.6)
Other	36 (16.5)	31 (14.6)
Number of transferred embryos		
2	165 (75.7)	155 (73.1)
3	53 (24.3)	57 (26.9)
Mode of fertilization		
Conventional IVF	143 (65.6)	140 (66.0)
ICSI	75 (34.4)	72 (34.0)

Comparable numbers of withdrawals were observed in both treatment groups. Overall, 163 (74.8%) of 218 women in the UTROGESTAN group withdrew prematurely, compared with 165

(77.8%) of 212 women in the 8% progesterone gel group. The reasons for withdrawal are given in Table 4.

Table 4: Reasons for discontinuation

Withdrawal reason	UTROGESTAN	Progesterone gel 8%
	n (% of study group)	% of study group
Pregnancy failure	153 (70.2)	150 (70.8)
Lack of β-hCG increase or start of menstrual bleeding	143 (65.6)	141 (66.5)
Abortion	3 (1.4)	6 (2.8)
Missed abortion	7 (3.2)	3 (1.4)
Other reasons for withdrawal	10 (4.6)	15 (7.1)
Adverse event	1 (0.5)	2 (0.9)
Local intolerance	1 (0.5)	3 (1.4)
Unallowed hormone therapy	4 (1.8)	3 (1.4)
Withdrawal of consent	-	2 (0.9)
Lost to follow-up	3 (1.4)	2 (0.9)
Other	1 (0.5)	3 (1.4)
Total Withdrawn	163 (74.8)	165 (77.8)

Study results

Table 5 - Results of Study #1

Primary Endpoints	**UTROGESTAN N= 218**	**Progesterone gel 8% N= 212**	**Treatment percentage difference (90% Confidence interval)**
Ongoing pregnancy rate at the end of the 12th week of gestation	25.2% (55/218)	22.2% (47/212)	3.1% (-3.9 – 10.0)

The primary endpoint was the ongoing pregnancy rate at the end of the 12th week of gestation in the per-protocol population. Ongoing pregnancy rates were 25.2% (95% confidence interval: 19.6-31.5) in the UTROGESTAN group and 22.2 % (95% confidence interval: 16.8-28.4) in the progesterone gel group. The ongoing pregnancy rate in patients treated with UTROGESTAN was non-inferior to the one in patients treated with Progesterone gel 8%. The rate difference was 3.1% (90% CI -3.9 - 10.0). According to the pre-specified criteria, the pregnancy rate in the Utrogestan group was demonstrated to be non-inferior to that in the progesterone gel group (lower limit of the 90% confidence interval > -0.1).

Similar numbers of implantations or living fetuses were recorded in both treatment groups. In total, 71% of pregnancies in the UTROGESTAN group and 79% in the progesterone gel (8% w/v) group were singleton pregnancies.

A very similar number of women experienced abortion or missed abortion in the UTROGESTAN (4.6%) and the progesterone gel (8% w/v) (4.2%) groups.

DETAILED PHARMACOLOGY

Clinical Pharmacology

Administered vaginally, progesterone may undergo a uterine pass effect as suggested by higher uterine tissue progesterone concentrations after vaginal administration than seen in intramuscular (IM) administration.
In blood, progesterone is largely (95- 98%) bound to plasma proteins. The 3 primary progesterone- binding proteins in plasma are albumin, cortisol-binding globulin (CBG), and sex hormone-binding globulin (SHBG), with albumin being predominant progesterone- binding protein. Progesterone is primarily metabolized through reduction processes.

Progesterone is metabolized hepatically to pregnanediol and conjugated with glucuronic acid. Approximately 50-60% of metabolite excretion occurs via the kidney and an additional 10% of metabolites are excreted via the bile. Progesterone metabolites excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

Because progesterone is primarily metabolized through reduction process, hydroxylation processes and therefore the potential role for CYP isoforms, which catalyze oxidative biotransformations, play a minor role. Drug interactions have not been identified with other progesterone vaginal products. There is no evidence that progesterone treatment, especially when given vaginally, will clinically significantly affect the metabolism of other drugs administered concomitantly. Other drugs administered concomitantly with Utrogestan are not expected to affect Utrogestan metabolism in a clinically significant way.

TOXICOLOGY

The toxicology of micronized progesterone has been studied in a number of animal species, including mice, rats, rabbits and dogs.

Single-Dose Toxicity

Progesterone demonstrated a very low order of acute toxicity. In rats the oral LD_{50} was 1,000 to 2,000 mg/kg in males and 320 to 400 mg/kg in females. In rabbits, the intravenous LD_{50} was 26.5 mg/kg.

For the neonate mouse, the subcutaneous LD_{50} progressed with age from 70 mg/kg in 0 to 24 hour old mice to 2,700 mg/kg in 121 to 168 hour old mice.

Repeat-Dose Toxicity

In rats, oral administration of progesterone at doses up to 250 mg/kg/day for 4 weeks and up to 135 mg/kg/day for 12 weeks resulted in signs of sedation, relaxation and coma at the highest dose levels (135 and 250 mg/kg/day), salivation at 100 mg/kg/day and dose related weight gain in females at 100 and 250 mg/kg/day.

In a 26-week study in rats, subcutaneous administration of progesterone revealed toxic effects only at the highest dose of 16 mg/kg/day with atrophy of the gonads, uterus and prostate and, in males, increased pituitary weight. Oral administration led to virtually no effects (NOEL of 160 mg/kg/day).

In dogs, the repeat-dose oral toxicity of micronized progesterone was studied at daily doses of 50, 125 and 325 mg/kg for 12 weeks, where no mortalities were observed at any dose level. Animals receiving 325 mg/kg experienced treatment related effects of irritability and sedation. Serum biochemical alterations occurred at all levels of treatment, including changes in serum cholesterol, lipoproteins, total lipids and electrolyte balance. Target tissue effects included histopathological findings such as mammary gland adenoma, ovarian cysts and cystic dysplasia of the endometrium. Treatment related histological changes were not observed in other tissues.

Treatment of monkeys for one year with vaginal rings releasing 235 or 1,770 µg progesterone/day showed effects on organs of the reproductive system at both dose levels.

Mutagenicity

Progesterone did not induce genotoxicity in a range of *in vitro* and *in vivo* investigations.

Studies on transformation in rodent cells *in vitro* were inconclusive, with a rat embryo cell study giving a positive result, a mouse cell study giving a weak positive result and a Syrian hamster embryo cell study giving a negative result.

Carcinogenicity

Some evidence of reproductive tissue carcinogenicity (ovarian, uterine and mammary) was observed in mice, and pre- neoplastic mammary gland nodules were seen in dogs after chronic treatment. Progesterone is known to increase the tumour incidence in endocrine target tissues after continuous (parenteral) doses clearly above the physiological levels.

Reproductive and Developmental Toxicity

A Clauberg-McPhail test in rabbits, established an oral hormonal NOEL of 3.2 mg/kg/day, while the subcutaneous NOEL was 0.025 mg/kg/day. The findings of a hormonal effect at such doses is to be expected, and is consistent with the therapeutic hormonal role of progesterone.

Progesterone administered intramuscularly to rats at a dose of 5 mg/day on gestation days (GD) 16 to 19 had no effect, but the same dosage on GD 20 to 23 caused fetal death, which was probably related to the prolonged delay of parturition due to progesterone administration.

Reproductive studies have been performed in mice at doses up to 9 times the human oral dose, in rats at doses up to 44 times the human oral dose, in rabbits at a dose of 10 µg/day, in guinea pigs at doses of approximately one-half the human oral dose and in rhesus monkeys at doses approximately the same as the human dose (all based on body surface area). These studies have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

Administration of progesterone by SC injection to pregnant mice resulted in a decrease in sexual behavior in male offspring with no changes to internal or external genitalia, and an increase in aggressive behavior in female offspring. No abnormalities of internal or external genitalia were observed in the offspring of rats treated with progesterone by SC injection.

Local Tolerance

An intravaginal repeat dose local tolerance study was performed in adult female New Zealand White rabbits using Utrogestan capsules. Groups of six adult female rabbits received 33 mg/day progesterone (1/3 capsule) or placebo (1/3 capsule) daily for 29 consecutive days. A third group of six females served as absolute controls.

There were no treatment-related deaths and no clinical signs of adverse effects. Examination of the vulva revealed no adverse treatment-related local tolerance findings, with no treatment-related increases in vulvar erythema. As well, there were no adverse effects on the body weight, development or food consumption. There were no macroscopic or microscopic abnormalities attributable to treatment.

The findings from the study show no evidence of any local tolerance concerns after repeated intravaginal treatment with Utrogestan at a daily dose comparable to the maximum clinical dose of 600 mg/day for women of approximately 60 kg body weight.

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PART III: CONSUMER INFORMATION

UTROGESTAN
Progesterone Vaginal capsules

This leaflet is part III of a three-part "Product Monograph" published when UTROGESTAN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about UTROGESTAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
UTROGESTAN is used in women undergoing treatment for *in vitro* fertilization (IVF).

What it does:
The progesterone in UTROGESTAN helps you to become pregnant and to stay pregnant.

When it should not be used:
Do not use UTROGESTAN if you:

- are allergic to progesterone, soybean lecithin, gelatin or any of the other ingredients in UTROGESTAN;
- have liver disease;
- have unusual vaginal bleeding that has not been diagnosed by your doctor;
- have had or are having a stroke or a heart attack or if you have coronary artery disease (an obstruction of the blood vessels that supply the heart muscle);
- have a sudden and severe headache;
- you have partial or complete loss of vision;
- have or have had blood clots in the leg, lungs, eyes, or elsewhere in the body;
- have or have had thrombophlebitis (inflammation of the veins);
- have breast cancer or are suspected to have breast cancer;
- have or are suspected to have endometrial, ovarian, cervical or vaginal cancer ;
- have porphyria (a blood disease).

What the medicinal ingredient is:
Progesterone

What the nonmedicinal ingredients are:
Gelatin, glycerol, soybean lecithin, sunflower oil, titanium dioxide.

What dosage forms it comes in:
Soft gelatin vaginal capsules
200 mg progesterone per capsule.

WARNINGS AND PRECAUTIONS

BEFORE you use UTROGESTAN talk to your doctor or pharmacist if you:

- have a history of seizures or epilepsy;
- have asthma;
- have kidney disease;
- have heart disease;
- are using other products that are applied to your vagina, like those used to treat yeast infections;
- are older than 35 years of age;
- smoke;
- have edema (fluid retention).

IINTERACTIONS WITH THIS MEDICATION

Drugs that may interact with UTROGESTAN include:

- Bromocriptine, a drug used to treat problems with the pituitary gland and used to treat Parkinson's disease.
- Carbamazepine, a drug used to treat seizures and used to treat nerve pain.
- Cyclosporin a drug used to suppress the immune system.
- Antibiotics such as rifampicin which is a drug used to treat bacterial infections like tuberculosis.
- Ketoconazole,a drug used to treat fungal infections.
- Other products that are applied to your vagina, like those used to treat yeast infections.

Tell your doctor or pharmacist if you are taking, or have been taking, any other medicines, even medicines you buy without a prescription, and natural health products

PROPER USE OF THIS MEDICATION

How to take UTROGESTAN:

- Follow the directions given to you by your

doctor.

- Insert it deep into your vagina using your finger.
- Wash your hands before and after inserting UTROGESTAN.
- Wearing a panty liner is recommended, as sometimes there may be some leakage from the dissolved capsule.
- Do not take it by mouth.

Usual dose:

- One UTROGESTAN vaginal capsule inserted into the vagina three times a day, at morning, lunchtime and bedtime, or as directed by your doctor.
- You will start taking UTROGESTAN the day of embryo transfer.
- Continue taking UTROGESTAN until your doctor has checked to see if you are pregnant.
- If your doctor has confirmed that you are pregnant, you should continue taking UTROGESTAN three times a day until at least the 7th week of pregnancy but not later than the 12th week of pregnancy.
- Your doctor will tell for how long you should continue taking UTROGESTAN.

Overdose:

If you think you have taken too much UTROGESTAN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of UTROGESTAN take it as soon as you remember.
- Do not insert a double dose to make up for a forgotten dose.
- Do not insert more than three tablets a day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Occasionally, UTROGESTAN may cause local itching, burning, redness, or vaginal discharge. Talk to your doctor or pharmacist if these side effects worsen.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek Immediate Emergency Medical Attention
		Only if severe	In all cases	
Common	Nausea	✓		
	Vomiting	✓		
	Abdominal Pain	✓		
	Ovarian Hyperstimulation Syndrome (OHSS) weight gain, bloating or fluid retention in abdomen, nausea, vomiting, pelvic pain		✓	
	Vaginal spotting or bleeding	✓		
Uncommon	Allergic Reaction: rash, hives, itchiness, swelling of face, lips or throat, difficulty swallowing or breathing.			✓
	Vaginal Irritation	✓		
	Stroke: sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, weakness or numbness in an arm or leg.			✓

This is not a complete list of side effects. For any unexpected effects while taking UTROGESTAN, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15- 30°C. Do not refrigerate or freeze. Keep out of the reach and sight of children.

Do not use UTROGESTAN after the expiry date stated on the packaging. The expiry date refers to the last day of that month.

Store in the original blister pack and in the original outer carton.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.website.document or by contacting the sponsor, Besins Healthcare S. A., at: 1-800-XXX-XXXX

This leaflet was prepared by Besins Healthcare S. A..
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