Product Monograph

Including Patient Medication Information

Pr**UTROGESTAN®**

progesterone vaginal soft capsules

For vaginal use

200 mg

Progestin

Besins Healthcare S. A.

Rue Washington 80
1050 Ixelles
Belgium

Date of Authorization:
2026-04-02

Canadian Distributor / Importer Name and Address:

Organon Canada Inc.

16766 route Transcanadienne

Kirkland, Quebec

H9H 4M7

Control Number: 302796

Recent Major Label Changes

2 CONTRAINDICATIONS	2026-04
7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations; 7.1.1 Pregnant Women; 7.1.2 Breast-feeding; 7.1.3 Pediatrics; 7.1.4 Geriatrics	2026-04

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

UTROGESTAN (progesterone) is indicated for:

- luteal phase support during *in vitro* fertilization (IVF) cycles

1.1. Pediatrics

Pediatrics (<18 years): This drug is not intended for pediatric use and no clinical data have been collected in children

1.2. Geriatrics

Geriatrics (>65 years of age): No clinical data have been collected in patients over age 65.

2. 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, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging 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

4. Dosage and Administration

4.2. 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 12^{t}h week of pregnancy.

4.4. Administration

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

4.5. 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.

5. Overdose

Symptoms of overdosage may include somnolence, dizziness, euphoria or dysmenorrhoea which have been observed mainly following oral administration and to a much lower extent following vaginal administration.

Treatment of overdosage consists of decreasing the dose or discontinuation of progesterone vaginal soft capsules, and observation together with institution of appropriate symptomatic and supportive care

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
vaginal	Soft capsule / 200 mg / micronized progesterone	gelatin, glycerol, purified water, soybean lecithin, sunflower oil, titanium dioxide

Description

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

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

7. 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.
- A complete medical examination must be performed regularly during the treatment.
- 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.
- The pathologist should be informed of progesterone therapy when relevant specimens are submitted.
- 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 9.4 Drug-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 imminent premature labour. It must only be used in accordance with the indications of use see 1 Indications.
- Progesterone use should be discontinued if a non-viable pregnancy (missed abortion) or ectopic pregnancy is diagnosed.

Each Progesterone Soft Capsule 200 mg contains 2 mg soya lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients) (see 2 Contraindications). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Progesterone Soft Capsules.

Progesterone Soft Capsules contain highly refined oil, for which the incidence of hypersensitivity is very rare in adults

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.

Endocrine and Metabolism

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.

Hepatic/Biliary/Pancreatic

Cautious use in patients with mild to moderate hepatic dysfunction.

Psychiatric

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

7.1. Special Populations

7.1.1. 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.

7.1.2. Breastfeeding

UTROGESTAN is not indicated during lactation. Detectable amounts of progesterone enter the breast milk. Progesterone is excreted in human milk to such an extent that the effects on the breastfed newborns / infants are likely.

7.1.3. Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Local intolerance (burning, pruritus or fatty discharge) has been observed during the different clinical trials and reported in the literature but incidences were extremely low. 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 with progesterone vaginal soft capsules at the recommended dosages.

The adverse reactions listed below are based on post-marketing data and clinical trials.

- **Gastrointestinal disorders**

  Abdominal distension (including discomfort); abdominal pain (including upper and lower abdominal pain); nausea; constipation; diarrhoea; vomiting.

- **General disorders and administration site conditions**

  Fatigue; oedema (including peripheral swelling); burning sensation.

- **Infections and infestations**

  Vulvovaginal mycotic infection.

- **Metabolism and nutrition disorders**

  Fluid retention; weight fluctuation

- **Musculoskeletal and connective tissue disorders**

  Back pain; muscle spasms.

- **Nervous system disorders**

  Dizziness; headache; somnolence; migraine.

- **Psychiatric disorders**

  Insomnia; depression; nervousness.

- **Renal and urinary disorders**

Dysuria.

- **Reproductive system and breast disorders**

  Breast discomfort (including pain, swelling, discomfort and tenderness); vaginal discharge; vaginal haemorrhage; vulvovaginal discomfort; menstrual cycle abnormal.

- **Skin and subcutaneous tissue disorders**

  Pruritus; rash (including rash erythematous and pruritic); acne; alopecia; eczema; erythema; urticaria.

Common undesirable effects

Common known undesirable effects following vaginal exposure include insomnia, dizziness, headache, somnolence, abdominal distension, abdominal pain, nausea, pruritus, rash, breast discomfort, vaginal discharge, vaginal haemorrhage and fatigue.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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 2.

Table 2 – Adverse Events That Occurred in ≥ 1% Of Patients, In Both Treatment[1] Groups, In A Randomized, Controlled, Open Label, Comparative Clinical Trial

System organ class/preferred term	UTROGESTAN n = 28 (%)	Progesterone gel 8% n = 212 (%)
Digestive		
Nausea or emesis	1	0
Genitourinary		
Ovarian hyperstimulation syndrome	3	4
Sexual Function/Reproduction		

System organ class/preferred term	UTROGESTAN n = 28 (%)	Progesterone gel 8% n = 212 (%)
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%).

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

There is no relevant use of UTROGESTAN in women less than 18 years.

8.5. Post-Market Adverse Reactions

The following common adverse reactions have been identified during post-approval use of UTROGESTAN administered vaginally.

Gastrointestinal disorders: nausea, abdominal pain / distension

Nervous system disorders: dizziness, headache, somnolence

Psychiatric disorders: insomnia

Skin and subcutaneous tissue disorders: pruritus, rash

Reproductive system and breast disorders: breast discomfort, vaginal discharge / haemorrhage

General disorders and administration site conditions: fatigue

9. Drug Interactions

9.3. Drug-Behaviour Interactions

The interaction of UTROGESTAN with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted for UTROGESTAN.

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.

Interactions associated with both vaginal and oral progesterone are listed below.
Enzyme inhibitors can alter the metabolism of progesterone, thereby increasing or decreasing progesterone levels.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Enzyme inhibitors: ▫ Antifungals (fluconazole, itraconazole, ketoconazole, and voriconazole) ▫ Immunosuppressants (tacrolimus) ▫ Statins (atorvastatin, rosuvastatin) ▫ Monoamine oxidase inhibitors (selegiline)	T	Can reduce the metabolism of progesterone, thereby increasing the bioavailability of progesterone levels	The clinical relevance of the i*n vitro* findings is unknown
Drugs known to induce the hepatic enzyme CYP450-3A: ▫ Barbiturates ▫ Anti-epileptic drugs (e.g., carbamazepine, efavirenz, eslicarbazepine, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide) ▫ Phenylbutazone ▫ Bromocriptine ▫ Spironolactone	T	May increase the metabolism and elimination of progesterone	The clinical relevance of the i*n vitro* findings is unknown

▫ Antiretrovirals (protease inhibitors) (e.g., darunavir, nelfinavir, fosamprenavir, and lopinavir) ▫ Antifungals (griseofulvin) ▫ Herbal product containing St John's Wort (Hypericum perforatum) ▫ Bosentan ▫ Aprepitant ▫ Rifamycin (rifampicin)			
▫ Ciclosporin	T	Progesterone may raise the plasma concentration of ciclosporin and the associated risk of toxicity The proposed mechanism is a competitive inhibition of ciclosporin metabolism via CYP450 3A4	The clinical relevance of the i*n vitro* findings is unknown
Diabetic medications	C / T	Progesterone can influence the control of diabetes mellitus	Progesterone-only steroids have been associated with an increase of Type 2 diabetes. An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with progesterone (see section warning)
Anticoagulants	T	Progesterone may enhance or reduce the anticoagulant effect of	

		coumarins. Progesterone antagonises the anticoagulant effect of phenindione	
Benzodiazepine derivatives	T	Progesterone may increase the plasma concentration of benzodiazepine derivatives such as diazepam, chlordiazepoxide and alprazolam, and induce glucoronidation of oxazepam and lorazepam	These synergistic effects are probably not clinically significant, because the therapeutic spectrum of benzodiazepines is wide
Tizanidine	T	Progesterone may increase the plasma concentration of tizanidine	The clinical relevance of this theoretical consideration is unknown
Emergency contraceptives	T	The concomitant use of ulipristal acetate with progesterone is expected to result in reduced efficacy of progesterone	The emergency contraceptive pill, ulipristal acetate (UPA), is a progesterone receptor agonist / antagonist

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; PBPK = Physiologically based pharmacokinetic modeling; popPK = Population pharmacokinetic modeling

9.7. 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.

10. 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.

10.1. 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.

10.3. Pharmacokinetics

Absorption

A randomized, crossover study compared the plasma bioavailability of progesterone after single dose vaginal administration of 200 mg UTROGESTAN vaginal soft 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 C_{max} were calculated after adjustment to endogenous progesterone):

Table 4 - Mean (±SD) Plasma Pharmacokinetic Parameters for Progesterone Following Single dose Vaginal Administration of UTROGESTAN 200 mg Soft Capsule or 1.125 g of Progesterone Gel 8%

Parameter	UTROGESTAN	Progesterone 8% Gel	Ratio or *Difference (90% Confidence Interval)
$C_{\delta max}$	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_{δ}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 ($C_{\delta max}$) 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 T_{max} 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.

Elimination

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.

Special populations and conditions

- **Pediatrics (<18 years):** No studies have been conducted to investigate the pharmacokinetics of progesterone in pediatric patients
- **Geriatrics (>65 years of age):** No studies have been conducted to investigate the pharmacokinetics of progesterone in geriatric patients

11. Storage, Stability, and Disposal

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

Part 2: Scientific Information

13. Pharmaceutical Information

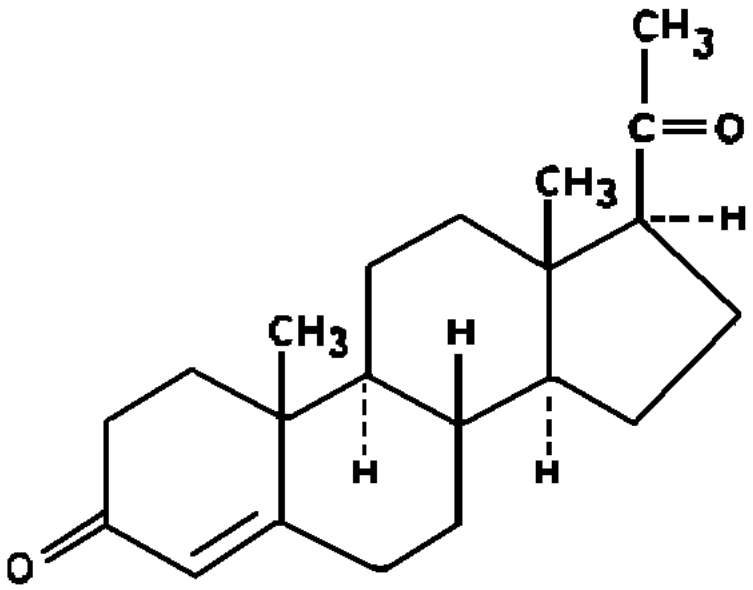
Drug Substance

Non-proprietary name of the drug substance: Progesterone

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

Molecular formula and molecular mass: $C_{21}H_{30}O_2$ and 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.

Pharmaceutical standard: Progesterone CRS issued by the European Pharmacopeia

14. Clinical Trials

14.1. Clinical Trials by Indication

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 5 – Summary of Patient Demographics for Clinical Trials in IVF

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
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 6.

Table 6: Demographic data, infertility, and Assisted Reproductive Technology-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 (65.5)	140 (66.0)
ICSI	75 (34.3)	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 7.

Table 7 – 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)

Table 8 – 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.

16. Non-Clinical Toxicology

General 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 LD50 was 1,000 to 2,000 mg/kg in males and 320 to 400 mg/kg in females. In rabbits, the intravenous LD50 was 26.5 mg/kg.

For the neonate mouse, the subcutaneous LD50 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.

Genotoxicity: 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 toxicology: 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 soft capsules. Groups of six adult female rabbits received 33 mg/day progesterone (1/3 soft capsule) or placebo (1/3 soft 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]UTROGESTAN®

progesterone vaginal soft capsules

This Patient Medication Information is written for the person who will be taking **UTROGESTAN**. This maybe you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **UTROGESTAN**, talk to a healthcare professional.

What UTROGESTAN is used for:

UTROGESTAN is used in women undergoing treatment for *in vitro* fertilization (IVF). It is used to support part of the menstrual cycle called the luteal phase.

How UTROGESTAN works:

The progesterone in UTROGESTAN helps to prepare the lining of the uterus for pregnancy and helps to maintain a pregnancy.

The ingredients in UTROGESTAN are:

Medicinal ingredient: progesterone

Non-medicinal ingredients: gelatin, glycerol, purified water, soybean lecithin, sunflower oil, titanium dioxide.

UTROGESTAN comes in the following dosage form:

Soft capsules: 200 mg

Do not use UTROGESTAN if you:

- are allergic to progesterone, soybean lecithin, gelatin, peanuts, or any of the other ingredients in UTROGESTAN (see **The ingredients in UTROGESTAN are:**)
- have severe liver problems or disease
- have abnormal or undiagnosed vaginal bleeding
- are pregnant but the baby has died in your womb (missed abortion) or implantation happened outside of the uterus (ectopic pregnancy)
- have recently had or are having a stroke or a heart attack
- have or have a history of cerebrovascular disease (a condition that affects blood flow to the brain)
- 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 or are suspected to have breast cancer
- have or are suspected to have endometrial, ovarian, cervical or vaginal cancer
- have porphyria (a blood disease)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take UTROGESTAN. Talk about any health conditions or problems you may have, including if you:

- have a history of seizures or epilepsy
- have a history of migraine headaches
- have partial or complete vision loss due to blood vessel disease of the eye
- have asthma
- have heart or kidney problems
- have diabetes
- have a history of depression
- are using other vaginal products, like those used to treat yeast infections
- are older than 35 years of age
- smoke
- have edema (fluid retention)
- are breastfeeding. UTROGESTAN passes into breastmilk.

Other warnings you should know about:

Check-ups and monitoring: Before starting treatment with UTROGESTAN you should have a complete physical exam including examination of your breasts and pelvic organs and a PAP smear. You should see your healthcare professional regularly during treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with UTROGESTAN:

- medicines used to treat Parkinson's disease, such as selegiline, bromocriptine
- anti-epileptic medicines used to control seizures such as carbamazepine, efavirenz, eslicarbazepine, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide
- medicines used to suppress the immune system, such as cyclosporin, tacrolimus
- medicines called "benzodiazepines" used to treat anxiety and sleep problems, such as diazepam, lorazepam
- anticoagulants medicines called "blood thinners" used to prevent the formation of blood clots
- medicines used to treat diabetes
- antifungal medications used to treat fungal infections, such as ketoconazole, itraconazole, fluconazole, voriconazole, griseofulvin
- medicines used to treat HIV, such as darunavir, nelfinavir, fosamprenavir, lopinavir
- medicines used to lower high cholesterol, such as atorvastatin, rosuvastatin
- herbal products containing St John's wort (*Hypericum perforatum*) used to treat depression
- aprepitant, used to treat nausea and vomiting during chemotherapy
- bosentan, used to treat high blood pressure in the lungs
- rifampicin, an antibiotic medicine used to treat tuberculosis
- spironolactone, a diuretic or "water pill" used to treat heart problems
- tizanidine, a muscle relaxant used to treat multiple sclerosis and other nerve problems
- ulipristal acetate, the emergency birth control pill
- other vaginal products, like those used to treat yeast infections

How to take UTROGESTAN:

- Follow the directions given to you by your healthcare professional.

- You will start taking UTROGESTAN the day of embryo transfer.
- Continue taking UTROGESTAN until your healthcare professional has checked to see if you are pregnant.
- If your healthcare professional has confirmed that you are pregnant, continue taking UTROGESTAN until at least the 7th week of pregnancy but not later than the 12th week of pregnancy.
- Wash your hands before and after inserting UTROGESTAN.
- Insert the UTROGESTAN soft capsule deep into your vagina using your finger.
- Wearing a panty liner is recommended, as sometimes there may be some leakage from the dissolved soft capsule.
- UTROGENSTAN is for vaginal use. Do not take it by mouth.

Usual dose:

One UTROGESTAN soft capsule inserted into the vagina three times a day, at morning, lunchtime and bedtime, or as directed by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much UTROGESTAN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a dose of UTROGESTAN insert it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not insert two doses at the same time.

Possible side effects from using UTROGESTAN:

These are not all the possible side effects you may have when taking UTROGESTAN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- abdominal discomfort (distension, pain)
- constipation, diarrhea
- breast tenderness/swelling, pain
- dizziness (lightheadedness)
- fatigue, tiredness
- insomnia, sleepiness
- headache
- rash with or without itching
- swelling

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Nausea	✓		
Vomiting	✓		
Ovarian Hyperstimulation Syndrome (OHSS): weight gain, bloating or fluid retention in abdomen, nausea, vomiting, pelvic pain		✓	
Vaginal hemorrhage: unusual spotting or bleeding, heavy bleeding that can be sudden or severe, bleeding after intercourse, pain, passing clots		✓	
Uncommon			
Allergic reaction: rash, hives, itchiness, swelling of face, lips or throat, difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up			✓
Vaginal irritation: burning, itching, fatty discharge from the soft capsule	✓		
Stroke (bleeding or blood clot in the brain): sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, weakness or numbness in an arm or leg			✓
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light		✓	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
suicide. If you have a history of depression, your depression may become worse			
Vaginal yeast infection: itching, burning, soreness, irritation and a whitish-grey cottage cheese-like discharge		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store between 15- 30°C. Do not refrigerate. Keep out of 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.

If you want more information about UTROGESTAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); Organon Canada website www.organon.ca or by calling Organon Canada at 1-844-820-5468.

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