



Supporting a healthy pregnancy

The role of progesterone
in Assisted Reproductive
Technology (ART)

Crinone[®]
progesterone gel 8%

The desire for pregnancy

It's one of the most important, intimate, and life-changing decisions you and your partner can make: the decision to have a baby. You've planned for it and have been doing everything a motivated couple needs to do to make their dream a reality. But, you aren't pregnant, and you're wondering why.

Obstetricians/gynecologists (OB/GYNs) and their nurses are the usual starting point for seeking help. They can offer initial treatment and guidance, as well as referrals to infertility specialists. Together, this group of healthcare professionals can help women and their partners achieve the goal of pregnancy. The sooner you seek help, the more likely your chance for success.

For those who need specialized help, Assisted Reproductive Technology (ART) refers to the various treatments available to help women achieve their dreams of healthy pregnancies. Should you require specialized treatment, there are multiple centers across the United States ready to assist you. These clinics offer a variety of fertility treatments, including in vitro fertilization (IVF), intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI), donor oocyte, and frozen embryo transfer (FET). One of the most frequently used treatments is IVF. IVF is a process in which eggs are extracted from a woman, fertilized outside the body (with husband, partner, or donor sperm), and placed into the woman's uterus. IVF provides excellent chances for success in most cases.

Your doctor has prescribed CRINONE® 8% (progesterone gel) because it provides effective progesterone support. Whether a pregnancy is spontaneous or medically assisted, progesterone is one of the hormones essential for achieving and maintaining a healthy pregnancy. This brochure will help guide you through the use of CRINONE vaginal progesterone gel as a vital part of your fertility treatment. More than 50 million doses of CRINONE have been prescribed over the past decade. Its unique once-daily formulation for progesterone supplementation is easy to use and requires no needles or painful injections.



Important Safety Information

The most common side effects of CRINONE (progesterone gel) 8% include breast enlargement, constipation, drowsiness, nausea, headache, and pain in the pubic area. You should not use CRINONE 8% if you have any disorders involving blockage of your blood vessels, or a history of these disorders, miscarriages, vaginal bleeding that hasn't been diagnosed, liver problems or disease, or known or possible cancer of the breast or genital organs. You should discontinue use of CRINONE 8% if any symptoms occur that signal a blockage of your blood vessels. There is no evidence that CRINONE 8% will work in preventing miscarriage. Your doctor should examine your breasts and pelvic organs, as well as perform a Pap smear prior to prescribing CRINONE 8%. If you have vaginal bleeding during treatment with CRINONE 8%, your doctor should look for the cause. If you have conditions that cause fluid retention, a history or depression, or diabetes, your doctor should provide special attention to your care while you are using CRINONE 8%.

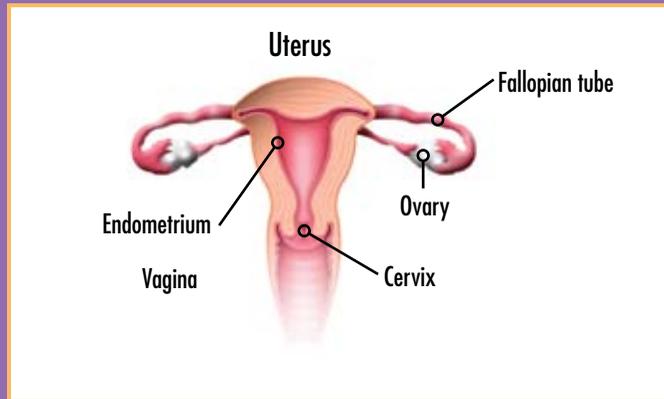
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Understanding your body

The reproductive system

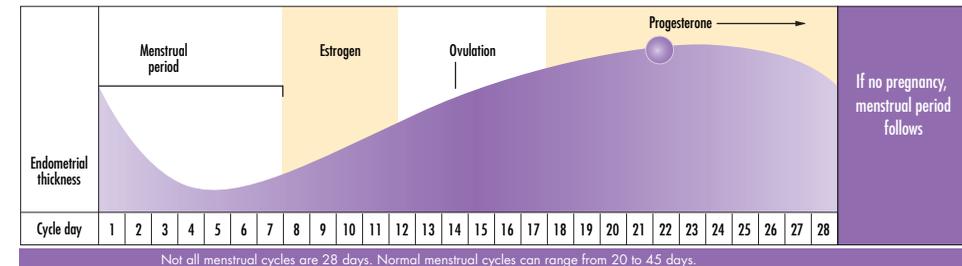
The “control center” of the reproductive system involves complex interactions between the brain and the ovaries. The hypothalamus (a region in the brain) sends chemical messages to the pituitary gland and ovaries, which in turn produce hormones that support the function of the other organs in the reproductive system. These other organs, as you’ll see below, include the fallopian tubes, the uterus, the cervix, and the vagina. Each organ has a specific function in the pregnancy process, and they all work together to achieve and sustain pregnancy.



The menstrual cycle—how your body prepares for pregnancy

The menstrual cycle plays an important role in reproduction. Every month it’s your body’s way of getting ready for a possible pregnancy. During this time, your ovaries will produce the hormone estrogen, which helps to strengthen the lining of the uterus (endometrium). The first day of your period marks the beginning of the cycle. If pregnancy did not occur in the previous cycle, the endometrium is shed. Most periods last from 4 to 7 days.

Once your period ends, the endometrium begins to thicken. For women with a 28-day menstrual cycle (cycle lengths vary among women), around the 14th day the ovary releases a mature egg. This process is known as ovulation.



During ovulation, a mature egg travels into the fallopian tubes and awaits fertilization by sperm. Once the egg is fertilized, it moves to the uterus and attaches to the endometrium (implantation).

The 12+ day time period following ovulation is called the luteal phase. The luteal phase is critical for preparing the endometrium for pregnancy. It is at the conclusion of the luteal phase that you will find out if you have become pregnant.

Progesterone and its role in pregnancy

Progesterone

Progesterone is a hormone produced by the ovaries and, later, if pregnancy occurs, by the placenta. Progesterone is essential to achieve and maintain a healthy pregnancy. In the second half of a woman's menstrual cycle, progesterone prepares the endometrium, or uterine lining, to receive the fertilized egg. If implantation is successful and pregnancy occurs, progesterone continues to support the uterine lining, providing the perfect environment for the growing embryo.

Progesterone plays 2 important roles:

1. Progesterone thickens and prepares the lining of the uterus for implantation of a fertilized egg.
2. After implantation, progesterone is required to maintain pregnancy.

Progesterone therapy in ART

If IVF or other ART treatments are recommended, fertility medications are almost always essential to the process. Certain medications and techniques typically used in the initial phase of ART can interfere with natural progesterone production; therefore, it is necessary to supplement, or in some cases replace, progesterone to ensure that the embryo is fully supported by the uterine lining.

Depending on the type of ART procedure recommended, your doctor will determine the amount of progesterone that is right for you and how long you should take it to maximize your chance for a successful pregnancy.



Pregnancy support with CRINONE

In the early days of ART, progesterone had to be administered by intramuscular injection. Fortunately, this is no longer the case. Advanced pharmaceutical research has developed CRINONE gel—a natural vaginal progesterone. Women have been enjoying the benefits and ease of vaginal progesterone for more than 10 years with CRINONE gel. CRINONE is the only FDA-approved once-daily vaginal progesterone available today.

CRINONE vaginal gel offers a generally well-tolerated, effective, and convenient way of getting this vital medication. In addition, by inserting the gel vaginally, the progesterone is transported directly to the uterus, where it is needed most—without first traveling through your entire body, as is the case with injections.

CRINONE also provides a benefit because it is designed to adhere to the vaginal wall, so CRINONE can be administered just once a day. This provides you with the most convenient progesterone treatment when compared to vaginal suppositories, capsules, or inserts—which require dosing 2 or 3 times a day.

CRINONE is a specially formulated once-daily gel containing natural progesterone.

CRINONE is a unique bioadhesive gel that coats and adheres to the vaginal walls after application. Progesterone is then absorbed into the vaginal wall and transported to the uterus, where it's needed most. CRINONE keeps a steady supply of progesterone going directly to the uterus throughout the day, providing effective, continuous progesterone support. What's more, CRINONE is generally well tolerated, convenient, and easy to use.

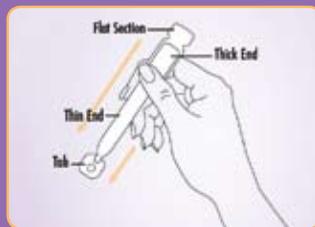


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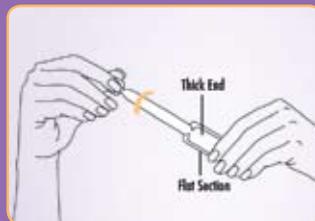
Instructions for using CRINONE

CRINONE comes in a slim, rounded vaginal applicator that is similar to that of a tampon. So, applying CRINONE is familiar and comfortable. Some gel will be left over in the applicator after use. You will still have received the dose you need.

- Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time (for women using CRINONE at altitudes above 2500 feet, see special instructions on page 13*)
- Hold the applicator between the thumb and forefinger along the seam on the thick end
- Shake down 3 to 4 times (like a thermometer) to ensure that the contents are at the thin end of the applicator



- Hold the applicator by the flat section of the thick end
- Twist off and throw away the tab at the thin end. Remember to twist off completely—do not pull the tab off
- DO NOT squeeze the thick end while twisting the tab. This could force some gel to be released before it is inserted into the vagina



- The applicator may be inserted into your vagina while you are in a sitting position or when lying on your back with your knees bent
- Gently insert the thin end well into your vagina



- Squeeze the thick end of the applicator to deposit CRINONE into the vagina
- Remove the applicator and throw it away in a waste container



***Special instructions for use at altitudes above 2500 feet:** Under certain rare circumstances, such as high altitude, brief exposure to high temperature, sudden changes in atmospheric or barometric pressure, and pressure-controlled environments such as airplanes or high-rise buildings, the internal pressure of the applicator may become higher than the surrounding air pressure. This imbalance between the internal and external pressure may cause the gel to expel from the applicator when the twist-off tab is removed.

After removing the applicator from the wrapper, hold the applicator on both sides of the thick end, or bulb. Using a lancet or a stick pin, make a single puncture in the flat part of the bulb. Place your thumb or finger over the puncture that you made in the applicator. This will relieve the difference in air pressure between the inside and the outside of the applicator caused by high altitudes. It will not affect the amount of progesterone administered. Follow the insertion steps above.

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Frequently asked questions

What time of day should CRINONE be administered?

If your doctor has prescribed CRINONE once a day: It can be administered once daily each morning which can make it easy for you to get up, use your CRINONE, and get on with your day.

If your doctor has prescribed CRINONE twice a day: It is recommended that you use CRINONE once in the morning and again in the evening.

Do I have to remain lying down after administration?

The applicator may be inserted into your vagina while you are sitting or lying on your back with your knees bent.

Will I experience any discharge?

Small, white globules may appear as a vaginal discharge possibly due to gel accumulation, even several days after usage. It is not unusual, but if you are concerned, discuss this with your doctor.

Some gel remains in the applicator following administration. Is this okay?

Yes. A small amount of gel will be left in the applicator after administration. This is normal; the proper dose will have been delivered.

Is it common to experience some bleeding?

A small amount of bleeding may occur in patients who are undergoing ART as well as women who experience a spontaneous pregnancy. There are many reasons why bleeding may occur. It is important to understand that bleeding before your pregnancy test does not mean the cycle has failed. Only your doctor, with the help of appropriate tests, can explain the meaning of any bleeding. Continue to use CRINONE as directed, and if you have any concerns, talk to your doctor.

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Frequently asked questions (cont)

Does CRINONE or the applicator cause vaginal irritation?

The CRINONE applicator has been specially developed for vaginal use, with a smooth, rounded tip designed so that there are no edges that could damage delicate tissue. Also, CRINONE does not contain perfumes or dyes, which are a known cause of vaginal irritation.

Does CRINONE require special storage or handling care?

CRINONE should be stored at 20-25°C (68-77°F). Do not expose CRINONE to extreme cold or heat. CRINONE does not require refrigeration or other special care. The individually wrapped applicators may be easily carried in a handbag for use when women are away from home.

Can CRINONE be used at the same time as other vaginal therapies?

CRINONE should not be applied at the same time as other local vaginal treatments. If other local intravaginal therapy is to be used, it should be administered at least 6 hours before or after CRINONE administration. Consult your doctor for more information about the specific drugs that have been prescribed for you.

When should CRINONE not be used?

- If you are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the gel (ask your pharmacist if you are not sure about the inactive ingredients in CRINONE)
- If you have unusual vaginal bleeding that has not been evaluated by a doctor
- If you have liver disease
- If you have known or suspected cancer of the breast or genital organs
- If you have had a miscarriage and your physician suspects some tissue is still in the uterus
- If you have or have had a blood clot in the legs, lungs, eyes, or elsewhere

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Additional patient resources

Below is a list of Web sites available to help you along the way. In addition to the support you receive from your team of healthcare professionals, you can learn more about CRINONE, ART, and infertility by visiting the following Web sites.

CRINONE

You can learn more about CRINONE and progesterone support by visiting www.crinoneusa.com

The following Web sites are not associated with www.crinoneusa.com. These resources are provided as a convenience to you, the patient. Watson Pharma, Inc., accepts no responsibility for the content or services offered by these organizations and their respective Web sites.

American Society for Reproductive Medicine (ASRM): Resources for Patients

ASRM provides information on infertility, menopause, contraception, reproductive surgery, endometriosis, and other reproductive disorders.

www.asrm.org

RESOLVE: The National Infertility Association

Established in 1974, RESOLVE is a nonprofit organization with the only established, nationwide network mandated to promote reproductive health and to ensure equal access to all family-building options for men and women experiencing infertility or other reproductive disorders.

www.resolve.org

The American Fertility Association

Founded in 1999, the American Fertility Association (AFA) helps support people trying to conceive and raises awareness around sexual and reproductive health and wellness. The AFA is a national nonprofit organization that provides information about infertility treatments, reproductive and sexual health, and family-building options, including adoption and third-party solutions.

www.theafa.org

Conceive Online and Conceive Magazine

Conceive endeavors to educate and empower women on their journey to parenthood through books, a magazine, and other resources through its Web site and its magazine.

www.conceiveonline.com

Society for Assisted Reproductive Technology (SART)

SART is the primary organization of professionals dedicated to the practice of ART in the United States. SART includes more than 392 member practices, representing more than 85% of the ART clinics in the United States. Its mission is to set and help maintain the standards for ART in an effort to better serve members and patients.

www.sart.org

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Glossary

Cervix: The lower portion of the uterus that provides an opening between the uterus and the vagina.

Donor oocyte: For women who cannot produce their own eggs or have poor egg quality, eggs may be available from women who choose to donate them. These eggs are called donor oocytes.

Embryo: The earliest stages of fetal development, from the moment of fertilization continuing through the eighth week of pregnancy.

Endometrium: The lining of the uterus, which develops throughout the menstrual cycle to accept and nourish the embryo after conception. During menstruation (a “period”), it is the endometrium that is being shed because pregnancy did not occur.

Estrogen: One of the hormones produced by the ovaries. It helps to build up the endometrium during the menstrual cycle. Some women may require estrogen supplementation or replacement therapy.

Fallopian tubes: The tiny tubes that join the ovaries to the uterus, through which a mature egg will travel at ovulation. Fertilization occurs in either one of these tubes.

Fertilization: Conception. Penetration of a mature egg by a sperm.

Frozen embryo transfer (FET): Frozen embryos can be used as a part of IVF therapy. Once a mature egg has been retrieved and fertilized with sperm, the embryo can be frozen for future use.

Implantation: The process of attachment of a fertilized egg to the endometrium.

Intracytoplasmic sperm injection (ICSI): After a mature egg is collected from the woman, sperm is inserted directly into the egg.

Intrauterine insemination (IUI): A common method of artificial insemination. An IUI involves the insertion of sperm directly into the uterus, which places the sperm closer to the egg for fertilization.

In vitro fertilization (IVF): Fertilization of an egg by sperm that occurs outside of the body. The fertilized egg is then placed into a woman’s uterus for implantation.

Menstrual cycle: The monthly cycle in which the endometrial lining of the uterus is first shed, then replenished to prepare for the next ovulation. If pregnancy does not occur after ovulation, the endometrial lining is shed (in the process known as the “period”) and the cycle begins again.

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Glossary (cont)

Ovaries: The pair of small organs where the eggs are stored and where the female hormone progesterone is produced.

Ovulation: The release of a mature egg from the ovary.

Placenta: The organ that develops during pregnancy that transports nutrients to the fetus and waste away from the fetus. The placenta is attached to the uterus and is connected to the fetus by the umbilical cord.

Progesterone: A hormone that plays 2 important roles in pregnancy: (1) thickens the endometrium to prepare for implantation of a fertilized egg, and (2) supports pregnancy through birth.

Progesterone replacement: Treatment with progesterone in women who do not produce progesterone.

Progesterone supplementation: Treatment with progesterone in women who produce low levels of progesterone.

Uterus: The muscular organ in which a fertilized egg implants and matures through pregnancy. During menstruation, the uterus sheds the inner lining.

Patient information

Crinone® 8%

(progesterone gel)
For Vaginal Use Only

FOR PROGESTERONE SUPPLEMENTATION OR REPLACEMENT AS PART OF AN ASSISTED REPRODUCTIVE TECHNOLOGY (“ART”) TREATMENT FOR INFERTILE WOMEN WITH PROGESTERONE DEFICIENCY

Please read this information carefully before you start to use CRINONE and each time your prescription is renewed, in case anything has changed. This leaflet does not take the place of discussions with your doctor. If you still have any questions, ask your doctor or health-care provider.

What CRINONE is

CRINONE is a specially formulated gel that you insert in your vagina. It contains the natural female hormone called progesterone. CRINONE 8% is used as part of a program for women who are undergoing fertility treatment.

Understanding the role of CRINONE in your infertility treatment

Progesterone is one of the hormones essential for maintaining a pregnancy. If you are undergoing ART treatment and your doctor has determined your body does not produce enough progesterone on its own, CRINONE may be prescribed to provide the progesterone you need.

The progesterone in CRINONE will help prepare the lining of your uterus so that it is ready to receive and nourish a fertilized egg. If pregnancy occurs, CRINONE may be supplemented for 10-12 weeks until production of progesterone by the placenta is adequate.

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When you should not use CRINONE

- If you are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the gel (ask a pharmacist if you are not sure about the inactive ingredients in CRINONE)
- If you have unusual vaginal bleeding which has not been evaluated by a doctor
- If you have a liver disease
- If you have known or suspected cancer of the breast or genital organs
- If you have a miscarriage and your physician suspects some tissue is still in the uterus
- If you have or have had blood clots in the legs, lungs, eyes, or elsewhere

Risks of CRINONE

- *Risk to the fetus.* Birth defects have been reported in the offspring of women who were using CRINONE during early pregnancy. These included an abdominal wall defect and a cleft palate. A causal association has been neither confirmed nor refuted. You should check with your doctor about the risks to your unborn child of any medication used during pregnancy.
- *Blood clots and related health problems.* Blood clots have been reported with the use of estrogens and progestational drugs (alone or in combination). If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to part of the brain), a heart attack (by cutting off blood to part of the heart), a pulmonary embolus (by cutting off blood to part of the lungs), or other problems. Any of these conditions may cause death or serious long-term disability. Call your doctor immediately if you suspect you have any of these conditions. He or she may advise you to stop using this drug.

PRECAUTIONS

Be alert for unusual signs and symptoms. If any of these warning signals (or any other unusual symptoms) happen while you are using CRINONE, call your doctor immediately:

- Abnormal bleeding from the vagina
- 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
- Breast lumps, which could be associated with fibrocystic disorders, fibroadenoma, or breast cancer. (Ask your doctor or healthcare provider to show you how to examine your breasts monthly)
- Yellowing of the skin and/or white of the eyes indicating possible liver problems

You should also notify your doctor if you experience depression, worsening of your diabetic condition, or fluid retention.

Possible side effects of CRINONE

In addition to the risks listed above, the following side effects have been reported with CRINONE used either for progesterone supplementation or for replacement as part of an ART treatment for infertile women with progesterone deficiency. Consult your doctor if you experience any of the side effects mentioned below, or other side effects.

SIDE EFFECTS REPORTED AT A FREQUENCY OF 5% OR GREATER

- Abdominal pain, perineal pain (the perineum is the area between the vagina and the rectum)
- Headache
- Constipation, diarrhea, nausea
- Joint pain

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- Depression, decreased libido, nervousness, sleepiness*
- Breast enlargement
- Excessive urination at night

SIDE EFFECTS REPORTED AT A FREQUENCY RANGING FROM 1% TO 5%

- Allergy, bloating, cramps, fatigue, pain
- Dizziness*
- Vomiting
- Mood swings
- Breast pain
- Difficult or painful intercourse, genital itching, genital yeast infection, vaginal discharge
- Urinary tract infection

SIDE EFFECTS REPORTED AT A FREQUENCY OF LESS THAN 1%

- Fever, flu-like symptoms
- Water retention†
- Gastrointestinal discomfort, gas, abdominal swelling
- Back pain, leg pain
- Insomnia
- Sinusitis, upper respiratory tract infection
- Asthma
- Acne, itching
- Painful or difficult urination, frequent urination

*If you experience dizziness or sleepiness, do not drive or operate machinery.

†This may worsen some conditions such as asthma, epilepsy, migraine, heart disease, or kidney disease.

How CRINONE works

CRINONE has been formulated to be administered through the vagina. The moisturizing gel in CRINONE forms a coating on the walls of the vagina, which allows for absorption of progesterone through the vaginal tissue. Small, white globules may appear as a vaginal discharge possibly due to accumulation, even several days after usage. CRINONE contains no irritating perfumes or dyes.

Other information

1. Your doctor has prescribed this drug for you and you alone.
Do not give this drug to anyone else.
2. This medication was prescribed for your particular medical condition.
Do not use it for another condition.
3. Keep this and all drugs out of the reach of children.

How to use CRINONE

The dosage is one application of the 8% gel (90 mg of progesterone) vaginally, daily or twice daily as directed by your doctor. If you become pregnant, your doctor may decide to continue treatment for up to 10 to 12 weeks.

CRINONE is to be applied directly from the specially designed sealed applicator into the vagina. The applicator is designed to deliver a premeasured dose of CRINONE. A small amount of gel will be left in the tube after usage. Do not be concerned because you will still be receiving the appropriate, measured dosage.

To report suspected adverse reactions, call 1-888-PROGEL8 (1-888-776-4358) or the FDA at 1-800-FDA-1088 (1-800-332-1088), or log on to www.fda.gov/medwatch or www.crinoneusa.com.

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For more information on CRINONE, visit www.crinoneusa.com.

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