Progesterones Step Therapy with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
02-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Crinone® 4% (progesterone) Vaginal gel	Secondary amenorrhea		1
Crinone® 8% (progesterone) Vaginal gel	Progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency Secondary amenorrhea in women who have failed to respond to treatment with Crinone 4%		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Secondary amenorrhea	Amenorrhea is the absence or abnormal cessation of the menses. Primary and secondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively. In women with regular menstrual cycles, a delay of menses for as little as one week may require the exclusion of pregnancy. Secondary amenorrhea is defined as the absence of menses for greater than 3 months in women that previously had regular menstrual cycles or 6 months in women who had irregular menstrual cycles.(3) The prevalence of amenorrhea not due to pregnancy, lactation or menopause is approximately 3-4%. The list of potential causes of amenorrhea is long, the majority of cases are caused by six conditions: polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, hypo- and hypergonadotropic hypogonadism, and anatomic abnormalities. The most common cause of secondary amenorrhea is pregnancy. After pregnancy is ruled out, the initial work-up should be based on patient history and physical examination. In addition to a history and physical, an estimation of follicle stimulating hormone (FSH) and estradiol will identify the most common causes of secondary amenorrhea. Patients presenting with amenorrhea should also have measurements of thyroid-stimulating hormone (TSH) and prolactin.(3)
Assisted Reproductive Technology	The modulating effects of progesterone on endometrial structure and function are essential to the success of human reproduction. After ovulation, progesterone produced by the corpus luteum (CL) induces "secretory" maturation of the endometrium, involving a cascade of molecular events that ultimately renders the endometrium receptive to implantation of the embryo. Considering the important role that progesterone plays in human reproduction, it is not surprising that exogenous supplemental progesterone is a common element of treatment regimens in infertility, particularly those relating to the assisted reproductive technologies (ART). To optimize endometrial receptivity, it is common practice to administer a progesterone

	supplement during the luteal phase. Progesterone supplementation is generally initiated on the day of oocyte retrieval or at the time of embryo transfer.(4) Treatment may be continued until placental autonomy is achieved, up to 10 weeks for Endometrin and up to 10 to 12 weeks for Crinone.(1,2) Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied.(1,2) Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.(2)
Efficacy	Crinone is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, polypropylene vaginal applicators.(1) Endometrin (progesterone) vaginal insert contains micronized progesterone. Endometrin is supplied with polyethylene vaginal applicators.(2)
Safety	Crinone is contraindicated in individuals with any of the following conditions:(1) • Known sensitivity to Crinone (progesterone or any of the other ingredients) • Undiagnosed vaginal bleeding • Liver dysfunction or disease • Known or suspected malignancy of the breast or genital organs • Missed abortions • Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders Endometrin is contraindicated in individuals with any of the following conditions:(2) • Previous allergic reactions to progesterone or any of the ingredients of Endometrin Vaginal Insert • Undiagnosed vaginal bleeding • Known missed abortion or ectopic pregnancy • Liver disease • Known or suspected malignancy of the breast or genital organs • Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events

REFERENCES

Number	Reference
1	Crinone prescribing information. Allergan, Inc. June 2017.
2	Endometrin prescribing information. Ferring Pharmaceuticals Inc. January 2018.
3	Current evaluation of amenorrhea: a committee opinion. *Fertility and Sterility*. 2024;122(1):52-61. doi:10.1016/j.fertnstert.2024.02.001
4	Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. *Fertility and Sterility*. 2008;89(4):789-792. doi:10.1016/j.fertnstert.2008.02.012

POLICY AGENT SUMMARY STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Crinone	Progesterone Vaginal Gel 4%	4 %	M ; N ; O ; Y	N		
Crinone	Progesterone Vaginal Gel 8%	8 %	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Crinone	Progesterone Vaginal Gel 4%	4 %	6	Applicators	30	DAYS			
Crinone	Progesterone Vaginal Gel 8%	8 %	60	Applicators	30	DAYS			

CLIENT SUMMARY – STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Crinone	Progesterone Vaginal Gel 4%	4 %	Commercial ; HIM ; ResultsRx
Crinone	Progesterone Vaginal Gel 8%	8 %	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Crinone	Progesterone Vaginal Gel 4%	4 %	Commercial ; HIM ; ResultsRx
Crinone	Progesterone Vaginal Gel 8%	8 %	Commercial ; HIM ; ResultsRx

STEP THERAPY CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Crinone 4%	**Target Agent(s)** **Crinone 4%** (progesterone) vaginal gel **Target Agent(s)** will be approved when ONE of the following is met: 1. The patient has been treated with ONE generic progesterone agent (e.g., oral contraceptives [combination or progestin only], micronized progesterone, intramuscular progesterone, norethindrone, medroxyprogesterone) in the past 90 days **OR** 2. The patient has an intolerance or hypersensitivity to ONE generic progesterone agent that is not expected to occur with the requested agent **OR** 3. The patient has an FDA labeled contraindication to ALL generic progesterone agents that is not expected to occur with the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.
Crinone 8%	**Target Agent(s)** **Crinone® 8%** (progesterone) vaginal gel **Target Agent(s)** will be approved when ONE of the following is met: 1. The patient has been treated with Endometrin in the past 90 days **OR** 2. The patient has been treated with the requested agent in the past 90 days **OR** 3. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** 4. The patient has an intolerance or hypersensitivity to Endometrin that is not expected to occur with the requested agent **OR** 5. The patient has an FDA labeled contraindication to Endometrin that is not expected to occur with the requested agent **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months