Progesterones Step Therapy with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
3/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Crinone® 4% (progesterone) Vaginal gel	• Secondary amenorrhea		1
Crinone® 8% (progesterone) Vaginal gel	• 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(3)	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 lasting three months and oligomenorrhea involving less than nine cycles a year require investigation. The prevalence of amenorrhea not due to pregnancy, lactation or menopause is approximately 3-4%. Although the list of potential causes of amenorrhea is long, the majority of cases are accounted for by four conditions: polycystic ovary syndrome hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure. History, physical examination, and estimation of follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and prolactin will identify the most common causes of amenorrhea. Patients with ovarian failure should be offered estrogen and progestin treatment to promote and maintain secondary sexual characteristics and reduce the risk of developing osteoporosis. 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 findings. Patients presenting with normal TSH and prolactin levels should be given a progestin challenge test to attempt to induce withdrawal bleeding. The overall goals of management in women with secondary amenorrhea include: correcting the underlying pathology, if possible, helping the woman to achieve fertility (if desired), and preventing complications of the disease process (e.g., estrogen replacement to prevent osteoporosis).
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) 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.(1-2)
Efficacy	**Crinone(1)** Crinone (progesterone gel) vaginal gel is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, polypropylene vaginal applicators.
Safety	**Crinone(1)** Crinone is contraindicated in patients with known sensitivity to Crinone (progesterone or any of the other ingredients), patients with undiagnosed vaginal bleeding, patient with liver dysfunction or disease, patients with known or suspected malignancy of the breast or genital organs, in missed abortions, or in patients with active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders.

REFERENCES

Number	Reference
1	Crinone Prescribing Information. Watson Pharma, Inc. June 2017
2	Current evaluation of amenorrhea. The practice Committee of the American Society for Reproductive medicine. Birmingham Alabama. Fertility and sterility Vol. 90, Suppl 3 November 2008.

Number	Reference
3	Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. The Practice Committee of the American Society for Reproductive Medicine. American Society for Reproductive Medicine, Birmingham Alabama Fertility and Sterility Vol 89, No 4, April 2008.

POLICY AGENT SUMMARY STEP THERAPY

Agent Names	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
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	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Crinone	Progesterone Vaginal Gel 4%	4 %	6.0	APPLCS	30	Days				
Crinone	Progesterone Vaginal Gel 8%	8 %	60.0	APPLCS	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%	**Crinone 4%** will be approved when ONE of the following of the following is met: 1. Information has been provided that 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 **Length of approval:** 12 months NOTE: Quantity Limit also applies, please refer to Quantity Limit criteria section below.
Crinone 8%	**Crinone 8%** will be approved when ONE of the following is met:

Module	Clinical Criteria for Approval
	1. Information has been provided that the patient has been treated with Endometrin in the past 90 days **OR** 2. Information has been provided that the patient has been treated with the requested agent in the past 90 days **OR** 3. The prescriber states that 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 also applies, please refer to Quantity Limit criteria section below.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**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) is greater than 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. Information has been provided to support 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. Information has been provided to support 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) is greater than the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months