Medical Drug Clinical Criteria

Subject:	Infertility and HCG Agents		
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Overview

This document addresses the use of injectable infertility agents, including protocols to treat women with ovulation disorders, drugs used as part of an Assisted Reproductive Technology (ART) treatment (most commonly through in vitro fertilization [IVF]), intrauterine insemination, and as treatment of male infertility with gonadotropins.

For the purposes of this document, infertility is defined clinically in women and men who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination. The diagnosis of male or female infertility requires evaluation of the couple versus a single individual.

Infertility Drug	Pharmacologic Actions
Menotropins: FSH and LH (Menopur)	• The follicle stimulating hormone (FSH) and luteinizing hormone (LH) present in menotropin products produce ovarian follicular growth and maturation in women without primary ovarian failure.
Follitropin and Urofollitropins: FSH (Follistim AQ, Gonal-f/ RFF)	• The FSH present in follitropin and urofollitropin products produce ovarian follicular growth and maturation in women without primary ovarian failure.
Human chorionic gonadotropins (hCG) Urinary-derived hCG (Pregnyl, Novarel and HCG generics) Recombinant hCG (Ovidrel)	• Sole use of menotropins, follitropins or urofollitropins will result in an undesirable endogenous LH surge and premature egg release. Administration of hCG after treatment with these products will suppress the LH surge, thus facilitating final follicular development, maturation, and ovulation.
GnRH antagonists (Cetrorelix acetate (Cetrotide), Ganirelix)	• Gonadotropin-releasing hormone (GnRH) antagonists are used to suppress premature luteinizing hormone (LH) surges during ART. LH surge suppression prevents eggs from being released prematurely. Protocols using GnRH antagonists are referred to as “short protocols” as these agents allow for shorter treatment times.
GnRH analogs or agonists (Lupron Depot® and generic leuprolide acetate)	• Administration results in an initial release of endogenous LH and FSH release, but chronic daily administration (as in ART) results in suppression of endogenous LH and FSH release. Pre-treatment with GnRH analogs in ART prevents the endogenous LH surge which would occur if menotropins, follitropin or urofollitropin were used alone. Protocols using GnRH analogs are referred to as “long protocols” as use of these agents results in longer treatment times.
Clomiphene citrate	• Clomiphene binds to estrogenic receptors and thus decreases the number of available receptors. The hypothalamus and pituitary respond to this antiestrogenic effect by releasing additional LH, FSH and gonadotropins, resulting in ovarian stimulation.
Progesterone vaginal supplementation or replacement (Crinone 8% gel, Endometrin vaginal inserts)	• Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone functions to maintain the pregnancy. Vaginal supplementation or replacement of progesterone is used in ART protocols for infertile women who require progesterone supplementation.

The use of progesterone 4% gel is considered not medically necessary as part of an Assisted Reproductive Technology treatment for an infertile individual who requires progesterone supplementation.

This document also discusses the non-infertility uses of human chorionic gonadotropins—Pregnyl, Novarel and generics, these are FDA indicated for Hypogonadotropic hypogonadism which is commonly seen in association with other pituitary hormone deficiency states caused by structural lesions of the hypothalamic-pituitary region.

The FDA label reads human chorionic gonadotropin has not been demonstrated to be effective adjunctive therapy in the treatment of obesity or weight loss. There is no substantial evidence that it increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or "normal" distribution of fat, or that it decreases the hunger and discomfort associated with caloric restricted diets.

These agents are also indicated for use in Prepubertal cryptorchidism not due to anatomical obstruction. In general, HCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following HCG administration is permanent, in most cases, the response is temporary. Therapy is usually instituted in children between the ages of 4 and 9.

Ovarian Preservation for Fertility during Chemotherapy

A 2013, and subsequent 2018 update of the American Society of Clinical Oncology clinical practice guideline on fertility preservation for individuals with cancer indicated that evidence was insufficient regarding the effectiveness of GnRH agonists and other means of ovarian suppression in fertility preservation. However, the most recent National Comprehensive Cancer Network (NCCN) Oncology Guidelines for Adolescents and Young Adults indicate that GnRH agonists may protect ovarian function and recommends fertility preservation for individuals diagnosed with cancer. Additionally, NCCN breast cancer guidelines indicate randomized trials have shown that ovarian suppression with GnRH agonist therapy given during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function. A 2017 Endocrine Society published treatment of gender-dysphoric /gender incongruent persons: An Endocrine Society Clinical practice guideline, recommends offering fertility preservation to adults or adolescents prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults.

Non-Infertility Uses of HCG Agents

Drug	Non-infertility Indications
Human chorionic gonadotropins (hCG) Urinary-derived hCG (Pregnyl, Novarel and HCG generics)	• Used in prepubertal cryptorchidism not due to anatomical obstruction; OR • Used in hypogonadotropic hypogonadism secondary to a pituitary deficiency in males

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Injectable Follicle Stimulating Hormones (Follistim AQ, Gonal-f, Gonal-f-RFF, or Menopur (menotropins)) for Ovarian Stimulation Alone or with Intrauterine Insemination

Requests for Follistim AQ, Gonal-f, Gonal-f-RFF, or Menopur may be approved for a maximum of 3 cycles, with or without intrauterine insemination in an infertile (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) individual if the following criteria are met:

I. Individual has a diagnosis of hypogonadotropic anovulatory disorders or hypopituitarism (these individuals will not respond to follicle stimulating hormone alone, but will require additional therapy with luteinizing hormone containing product such as human chorionic gonadotropins or will use a mixed follicle stimulating hormone/luteinizing hormone product like Menopur); **OR**
II. Individual has a diagnosis of normogonadotropin anovulatory disorders (such as polycystic ovary syndrome) or those with unexplained infertility (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) who have not ovulated or conceived after a prior trial of 3 cycles of clomiphene.

Requests for ovarian induction with Follicle Stimulating Hormones or Menopur (menotropins) may not be approved for the following:

I. Individual is receiving more than 3 ovulatory cycles of therapy; **OR**
II. Individual has a diagnosis of tubal occlusion or primary ovarian failure.

Injectable Follicle Stimulating Hormones (Follistim AQ, Gonal-f, Gonal-f-RFF, or Menopur (menotropins)), Pregnyl, Novarel (urinary derived human chorionic gonadotropins) for Ovarian Stimulation in Conjunction with In Vitro Fertilization or Intracytoplasmic Sperm Injection

Requests for Follistim AQ, Gonal-f, Gonal-f-RFF, Menopur, Ovidrel (recombinant human chorionic gonadotropin) or Pregnyl, Novarel (urinary derived human chorionic gonadotropins), with Lupron Depot (gonadotropin releasing hormone agonists) or leuprolide acetate

(immediate release) or gonadotropin-releasing hormone antagonists (Cetrotide (cetrorelix acetate), ganirelix) may be approved for a maximum of 3 cycles of ovarian stimulation in conjunction with in vitro fertilization or intracytoplasmic sperm injection in an infertile (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) individual or couple if the following criteria are met:

I. The couple has a diagnosis of severe male factor infertility; **OR**
II. The individual has a diagnosis of bilateral tubal occlusion; **OR**
III. The individual has a diagnosis of unexplained infertility that has not responded to ovarian induction therapy.

Injectable Follicle Stimulating Hormones (Follistim AQ, Gonal-f, Gonal-f-RFF, Menopur (menotropins), Pregnyl, Novarel (urinary derived human chorionic gonadotropins)), gonadotropin releasing hormone agonists (Lupron Depot, Eligard, leuprolide acetate immediate release), or gonadotropin-releasing hormone antagonists (Cetrotide (cetrorelix), ganirelix) for Preservation of Fertility

Requests for Injectable Follicle Stimulating Hormones (Follistim AQ, Gonal-f, Gonal-f-RFF, Menopur (menotropins), Pregnyl, Novarel (urinary derived human chorionic gonadotropins)), gonadotropin releasing hormone agonists (Lupron Depot, Eligard, leuprolide acetate immediate release), or gonadotropin-releasing hormone antagonists (Cetrotide (cetrorelix), ganirelix) may be approved if the following criteria are met:

I. Individual is using in the preservation of fertility in pre-menopausal women; **AND**
II. One of the following:
    A. Individual currently has a cancer diagnosis (NCCN 2A); **AND**
        1. Individual meets one of the following:
            a. Individual will receive chemotherapy for cancer with a curative intent; **OR**
            b. Individual will receive radiation therapy for cancer with a curative intent;

    OR

    B. Individual has a diagnosis of gender dysphoria/incongruence; **AND**
        1. Individual will be starting gender-affirming hormonal therapy; **OR**
        2. Individual is an adolescent who will be starting puberty suppression therapy.

Injectable Follicle Simulating Hormones (Follistim AQ, Gonal-f) for Male Infertility Associated with Hypogonadotropic Hypogonadism

Requests for Follistim AQ or Gonal-F in combination with human chorionic gonadotropins in an infertile (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) individual may be approved if the following criteria are met:

I. Individual has a diagnosis of hypogonadotropic hypogonadism with onset prior to completion of pubertal development.

Requests for the use of human chorionic gonadotropin alone or in combination with follicle stimulating hormone may be approved if the following criteria are met:

I. Individual is using to maintain spermatogenesis for an infertile (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) individual with post-pubertal acquired hypogonadotropic hypogonadism who have previously had normal sperm production.

Requests for the use of human chorionic gonadotropin alone or in combination with follicle stimulating hormone may be approved if the following criteria are met:

I. Individual is using to maintain spermatogenesis for an infertile (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple) individual with partial gonadotropin deficiency.

Progesterone Vaginal Supplementation or Replacement for Infertility Treatment --Crinone 8% gel, Endometrin vaginal insert

Requests for Crinone 8% gel, Endometrin vaginal insert may be approved if the following criteria are met:

I. Individual is using as part of an Assisted Reproductive Technology treatment; **AND**
II. Individual has a diagnosis of infertility (infertility defined clinically in men or women who cannot achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or 6 cycles of therapeutic donor insemination, diagnosed as a couple); **AND**
III. Individual requires progesterone supplementation.

Human chorionic gonadotropin (HCG) (Novarel, Pregnyl, and HCG generics) and Recombinant HCG (Ovidrel) for non-infertility uses

Requests for Pregnyl, Novarel or HCG generics may be approved if the following criteria are met:

I. Individual has a diagnosis of prepubertal cryptorchidism not due to anatomical obstruction; **OR**
II. Individual has a diagnosis of hypogonadotropic hypogonadism secondary to a pituitary deficiency in males.

Requests for the use of Human Chorionic Gonadotropins (Novarel, Pregnyl, and HCG generics) and recombinant HCG (Ovidrel) may not be approved for the following criteria:

I. Individual is using in the treatment of fatigue, obesity, weight loss, erectile or sexual dysfunction, performance enhancement, anti-aging, or chronic pain management; **OR**
II. All other indications not included above.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J0725	Injection, chorionic gonadotropin; per 1,000 USP units [Novarel, Pregnyl, Ovidrel]
J1950	Injection, leuprolide acetate (for depot suspension); per 3.75 mg [Lupron]
J3490	Unclassified drugs [when specified as cetrorelix acetate (Cetrotide), or other injectable for infertility treatment]
J8499	Prescription drug, oral, non-chemotherapeutic, NOS [when specified as clomiphene citrate (Clomid, Serophene)]
J9217	Leuprolide acetate (for depot suspension), 7.5 mg [Eligard, Lupron Depot]
S0122	Injection, menotropins; 75 IU [Menopur]
S0126	Injection, follitropin alfa; 75 IU [Gonal-F]
S0128	Injection, follitropin beta; 75 IU [Follistim]
S0132	Injection, ganirelix acetate; 250 mcg [Antagon]
J3490	Progesterone vaginal insert or gel [Crinone 8%, Endometrin, Crinone 4%]
ICD-10 Diagnosis	
	All diagnoses pend

Document History

Revised: 08/16/2024
Document History:

- 08/16/2024 – Select Review: add leuprolide acetate immediate release. Leuprolide acetate immediate release was not removed during 6/10/2024 update. No changes. Coding Reviewed: No changes.
- 06/10/2024 – Annual Review: Add clomiphene citrate criteria to document, remove leuprolide acetate immediate release, wording update. Coding Reviewed: Added HCPCS J9217 [Eligard, Lupron Depot].
- 06/12/2023 – Annual Review: wording and formatting changes for cetrorelix, define infertility in criteria, update gender incongruence, wording and formatting. Coding Reviewed: No changes.
- 06/13/2022 – Annual Review: Add fertility preservation criteria for gender dysphoria, wording and formatting. Coding Reviewed: No changes.
- 12/13/2021 – Select Review: Edit Fertility Preservation criteria. Coding Reviewed: No changes.
- 09/13/2021– Annual Review: Remove discontinued products (Bravelle, Milprosa, Prochieve), clarify leuprolide acetate immediate release product, clarify criteria for fertility preservation. Coding reviewed: Removed HCPCS J3355.
- 12/14/2020 – Select Review: Add criteria for use in the preservation of fertility in those receiving chemotherapy. Coding Review: No changes.
- 08/21/2020 – Annual Review: Add criteria for use of Milprosa vaginal system. Coding Reviewed: Added HCPCS J3490
- 02/21/2020 – Select Review: Add criteria for use of HCG agents in non-infertility uses. Coding Reviewed: No changes.

- 09/09/2019 – Annual Review: Administrative update to clinical criteria for use in hypogonadotropic hypogonadism for clarity. Remove “low-dose” from criteria when discussing follicle stimulating hormones. Coding Reviewed: Added Ovidrel to J0725
- 08/17/2018 – Annual Review: Initial review of CG-Drug-11. Remove PA criteria for clomiphene citrate.

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14. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on May 20, 2024.
    a. Adolescent and Young Adult Oncology. V2.2024. Revised July 7, 2023.
    b. Breast Cancer. V2.2024. Revised March 11, 2024.
    c. Survivorship. V1.2024. Revised March 29, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.