Infertility Injectable Agents

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

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Summary

Fertility problems are possible for both men and women. The cause can be found through physical exam, extensive medical and sexual history. Depending on the cause of infertility, there are different treatment options. Medications are one of the infertility treatment options available for both men and women. Medications can help correct ovulation problems in women and hormone problems in men. When treatment options, including injectable infertility agents, exceed the comfort level of a provider, the member should be referred to a specialist with expertise in diagnosis and treatment of infertility (e.g., reproductive endocrinologist)

NOTE: Coverage of injectable fertility medications varies depending on a member's benefit policy.

1. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.
2. Please refer to Oscar's Medical Clinical Guideline Number CG016 - Diagnosis and Treatment of Infertility for medical coverage criteria of infertility diagnostic and treatment services.
3. This Clinical Guideline only applies to members whose plan covers injectable agents listed in Table 1 for infertility treatments.
    a. The Plan requires that members be unable to use, or have tried and failed preferred agent(s) first.
    b. The use of these agents for other indications (e.g., cancer treatments, gender dysphoria treatments) may also be addressed in separate Clinical Guidelines.

Table 1: Infertility Injectable Agents

Drug	Brand Name	Classification
Follitropin beta	Follistim AQ	Gonadotropins
Follitropin alfa	Gonal-F	
Follitropin alfa	Gonal-F RFF	
Follitropin alfa	Gonal-F RFF Redi-ject Pen	
Chorionic Gonadotropin (Human)	Novarel	
Chorionic Gonadotropin (Recombinant)	Ovidrel	
Chorionic Gonadotropin (Human)	Pregnyl	
Human Chorionic Gonadotropin, HCG	-	
Menotropins	Menopur	
Leuprolide Acetate	-	Gonadotropin-Releasing Hormone Agonists

Cetrorelix Acetate	Cetrotide	Gonadotropin Releasing Hormone Receptor Antagonist
Ganirelix Acetate	Fyremadel	

Definitions

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Infertility" refers to an individual or couple unable to achieve a successful pregnancy, or requires medical intervention to achieve pregnancy. For individuals attempting pregnancy through regular unprotected intercourse or therapeutic donor insemination, infertility evaluation may be appropriate after 12 months without pregnancy when the individual expected to carry the pregnancy is under 35 years of age, or after 6 months when the individual expected to carry the pregnancy is 35 years of age or older.

Infertility may be caused by disease, dysfunction, or malformation.

- Primary infertility refers to infertility in an individual or couple with no prior established pregnancy.
- Secondary infertility refers to infertility in an individual or couple following a prior established pregnancy.

"Iatrogenic Infertility" refers to transient or permanent infertility caused by a necessary medical intervention such as chemotherapy, pelvic radiotherapy, gonadotoxic therapies, or the surgical removal of the reproductive organs for the treatment of disease or gender dysphoria.

"Pregnancy" refers to clinical pregnancy documented by ultrasonography, biochemical or histopathologic examination.

"[s]" indicates state mandates may apply.

Clinical Indications

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

Infertility

The Plan considers Infertility Injectable Agents medically necessary when ALL of the following criteria are met:

1. The requested medication is prescribed by or in consultation with a specialist with expertise in diagnosis and treatment of infertility (e.g., reproductive endocrinologist); *AND*
2. The member meets ONE (1) of the following:
    a. The member is a female and meets ALL of the following:
        i. Is 18 years of age or older; *and*
        ii. The medication is being used for ONE (1) of the following FDA approved or compendia supported indications:
            1. Induction of ovulation; *or*
            2. Inhibition of premature luteinizing hormone surges; *or*
            3. Multiple follicle development; *or*
            4. Preservation of fertility when a medical treatment will directly or indirectly lead to iatrogenic infertility; *and*
        iii. IF the request is for induction of ovulation, the member has tried and failed clomiphene citrate or other comparable estrogen modulator (e.g., letrozole)[s] OR is unable to use them due to ONE (1) of the following:
            1. Documented trial and failure of at least 3-6 cycles[s]; *or*
            2. Intolerance or contraindication; *or*
            3. Risk factor(s) for poor response (e.g., hypogonadotropic hypogonadism, hypothalamic amenorrhea); *or*
            4. Rationale provided as to why it is not clinically appropriate (e.g., advanced reproductive age, diminished ovarian reserve, urgent fertility preservation before gonadotoxic therapy); *and*
            5. Member is 40 years of age or older*; and*
        iv. Clinical chart documentation is submitted showing ALL of the following:
            1. Complete gynecologic and endocrinologic evaluation and diagnosis of cause of infertility; *and*
            2. Member is currently not pregnant; *and*
            3. A diagnosis of primary ovarian failure has been excluded; *and*
            4. The fertility status of the male partner has been evaluated when applicable (e.g., not applicable for single individuals, same-sex couples); *and*
            5. Medical conditions preventing pregnancy have been excluded or adequately treated *(medical conditions preventing pregnancy may include blocked fallopian tubes, hyperprolactinemia, thyroid, or adrenal disorders)*; *OR*
    b. The member is a male and meets BOTH of the following:
        i. The medication is being used for ONE (1) of the following FDA approved or compendia supported indications:

            1. Induction of spermatogenesis; *or*
            2. Hypogonadotropic hypogonadism; *or*
            3. Prepubertal cryptorchidism; *and*
        ii. Clinical chart documentation is submitted showing BOTH of the following:
            1. Complete medical and endocrinologic evaluation and diagnosis of cause of infertility; *and*
            2. The fertility status of the female partner has been evaluated when applicable; *AND*
3. The use of medication at the requested dosage or quantity, frequency, site of administration, and duration of therapy is supported by Food and Drug Administration (FDA) approved dosing, falls within dosing guidelines found in a compendia, or evidence-based literature.

If the above prior authorization criteria are met, the requested Infertility Injectable Agents will be approved for[s]:

- Up to 3 months for females; *or*
- Up to 6 months for males

Experimental / Investigational, unproven[s]

Infertility Injectable Agents for any other fertility problems is considered experimental, investigational, or unproven.

Applicable Billing Codes

Table 2	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
J3590	Unclassified biologics
J3490	Unclassified drugs
S0128	Injection, follitropin beta, 75 iu
S0126	Injection, follitropin alfa, 75 iu
J0725	Injection, chorionic gonadotropin, per 1,000 usp units
S0122	Injection, menotropins, 75 iu
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J9218	Leuprolide acetate, per 1 mg
S0132	Injection, ganirelix acetate, 250 mcg

Table 3	
ICD-10 codes considered medically necessary with Table 2 (CPT/HCPCS) codes if criteria are met:	
Code	*Description*
E23.0	Hypopituitarism
E29.1	Testicular hypofunction
N46.01	Organic azoospermia
N46.021	Azoospermia due to drug therapy
N46.022	Azoospermia due to infection
N46.023	Azoospermia due to obstruction of efferent ducts
N46.024	Azoospermia due to radiation
N46.025	Azoospermia due to systemic disease
N46.029	Azoospermia due to other extratesticular causes
N46.11	Organic oligospermia
N46.121	Oligospermia due to drug therapy
N46.122	Oligospermia due to infection
N46.123	Oligospermia due to obstruction of efferent ducts
N46.124	Oligospermia due to radiation
N46.125	Oligospermia due to systemic disease
N46.129	Oligospermia due to other extratesticular causes
N46.8	Other male infertility
N46.9	Male infertility, unspecified
N97.0	Female infertility associated with anovulation
N97.1	Female infertility of tubal origin
N97.2	Female infertility of uterine origin
N97.8	Female infertility of other origin

Table 3	
ICD-10 codes considered medically necessary with Table 2 (CPT/HCPCS) codes if criteria are met:	
Code	*Description*
N97.9	Female infertility, unspecified
Q53.00	Ectopic testis, unspecified
Q53.01	Ectopic testis, unilateral
Q53.02	Ectopic testes, bilateral
Q53.10	Unspecified undescended testicle, unilateral
Q53.111	Unilateral intraabdominal testis
Q53.112	Unilateral inguinal testis
Q53.12	Ectopic perineal testis, unilateral
Q53.20	Undescended testicle, unspecified, bilateral
Q53.211	Bilateral intraabdominal testes
Q53.212	Bilateral inguinal testes
Q53.22	Ectopic perineal testis, bilateral
Q53.9	Undescended testicle, unspecified
Z31.84	Encounter for fertility preservation procedure

References

1. Clinical Pharmacology [database on the Internet]. Elsevier Inc., 2023, www.clinicalpharmacology.com. Accessed June 2023.
2. DailyMed. Package Inserts. U.S. National Library of Medicine, National Institutes of Health (NIH), 2023, dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed June 2023.
3. Lexicomp Online Database [database on the Internet]. Lexicomp Inc., 2023, online.lexi.com. Accessed June 2022.
4. Micromedex Solutions [database on the Internet]. Truven Health Analytics, 2023, micromedex.com. Accessed June 2023.
5. Birnbaum, S. Approach to the Infertile Couple. Primary Care Medicine: Office Evaluation and Management of the Adult Patient. 8th ed., Wolters Kluwer, 2021, pp. 1049-1056.
6. Brannigan RE, Hermanson L, Kaczmarek J, Kim SK, Kirkby E, Tanrikut C. Updates to Male Infertility: AUA/ASRM Guideline (2024). Journal of Urology [Internet]. [cited 2024 Sep 12];0(0). Available from: https://doi.org/10.1097/JU.0000000000004180
7. Buckett W, Sierra S. The management of unexplained infertility: an evidence-based guideline from the Canadian Fertility and Andrology Society. Reprod Biomed Online. 2019 Oct;39(4):633-640. doi: 10.1016/j.rbmo.2019.05.023. Epub 2019 Jul 11.

8. Cetrotide (cetrorelix acetate for injection) [prescribing information]. Rockland, MA: EMD Serono, Inc. June 2024.
9. Ethics Committee of the American Society for Reproductive Medicine. 2021. Access to fertility services by transgender and nonbinary persons: an Ethics Committee opinion. Fertility and sterility, 115(4), 874–878. https://doi.org/10.1016/j.fertnstert.2021.01.049.
10. Follistim AQ (follitropin beta) injection [prescribing information]. Kenilworth, NJ: Organon USA Inc., a subsidiary of Merck & Co., Inc. March 2023.
11. Ganirelix acetate injection [prescribing information]. Jersey City, NJ: Organon USA LLC. September 2024.
12. Gonal-F (follitropin alfa) for injection. [prescribing information]. Rockland, MA: EMD Serono, Inc. November 2023.
13. Gonal-F RFF (follitropin alfa) for injection. [prescribing information]. Rockland, MA: EMD Serono, Inc. November, 2023.
14. Gonal-F RFF Redi-ject (follitropin alfa) for injection. [prescribing information]. Rockland, MA: EMD Serono, Inc. May 2024.
15. Klipstein, S., et al. Fertility Preservation for Pediatric and Adolescent Patients with Cancer: Medical and Ethical Considerations. Pediatrics, vol. 145, no. 3, 2020, e20193994. DOI: 10.1542/peds.2019-3994. (Reaffirmed 2022 Jul)
16. Lafferty, K., et al. Infertility: Understanding Investigation and Treatment Options. InnovAiT, vol. 13, no. 7, 2020, pp. 394-401. DOI: 10.1177/1755738020923714.
17. Legro, R.S., et al. Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome. N Engl J Med, vol. 371, 2014, pp. 119-129.
18. Lindsay, T.J., Vitrikas, K.R. Evaluation and Treatment of Infertility. American Family Physician, vol. 91, no. 5, 2015, pp. 308-14.
19. Lobo, R.A. Infertility: Etiology, Diagnostic Evaluation, Management, Prognosis. Comprehensive Gynecology. 8th ed., Elsevier, 2022, pp. 838-860.e5.
20. Menopur (menotropins for injection) [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc. February 2014.
21. Ovidrel (choriogonadotropin alfa injection) [prescribing information]. Rockland, MA: EMD Serono, Inc. June 2010.
22. Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Diagnosis and treatment of luteal phase deficiency: a committee opinion. Fertil Steril. 2021 Jun;115(6):1416-1423. doi: 10.1016/j.fertnstert.2021.02.010. Epub 2021 Apr 4.
23. Practice Committee of the American Society for Reproductive Medicine. Evidence-Based Treatments for Couples with Unexplained Infertility: A Guideline. Fertil Steril, vol. 113, 2020, pp. 305-22.
24. Practice Committee of the American Society for Reproductive Medicine. Fertility Evaluation of Infertile Women: A Committee Opinion. Fertility and Sterility, vol. 116, no. 5, 2021, pp. 1255-1265. DOI: 10.1016/j.fertnstert.2021.08.038. (Reaffirmed 2022 Jul)
25. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertility and sterility, 112(6), 1022–1033. https://doi.org/10.1016/j.fertnstert.2019.09.013.
26. Practice Committees of the American Society for Reproductive Medicine and Society for Reproductive Endocrinology and Infertility. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion. Fertil Steril. 2020 Jan;113(1):66-70. doi: 10.1016/j.fertnstert.2019.09.020. PMID: 32033726.
27. Pregnyl (chorionic gonadotropin) for injection [prescribing information]. Kenilworth, NJ: Organon USA Inc. March 2023.
28. Reindollar, R., et al. A Randomized Clinical Trial to Evaluate Optimal Treatment for Unexplained Infertility: The Fast Track and Standard Treatment (FASTT) Trial. Fertil Steril, vol. 94, 2010, pp. 888-899.
29. Schlegel, P.N., et al. Diagnosis and Treatment of Infertility in Men. AUA/ASRM Guideline. American Urological Association.

30. Smithson DS, Vause TDR, Cheung AP. No. 362-Ovulation Induction in Polycystic Ovary Syndrome. J Obstet Gynaecol Can. 2018 Jul;40(7):978-987. doi: 10.1016/j.jogc.2017.12.004.
31. Su, H. I., Lacchetti, C., et al. Fertility Preservation in People With Cancer: ASCO Guideline Update Journal of the American Society of Clinical Oncology. 2025;43(12);1488–1515. https://doi.org/10.1200/JCO-24-02782.

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