

HUMAN MENOPAUSAL GONADOTROPINS (HMG)

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Related Policy
<ul style="list-style-type: none"> Acquired Rare Disease Drug Therapy Exception Process Infertility Diagnosis and Treatment

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package (Medical) ² Pharmacy ²
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ¹
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	¹ Precertification through Optum is required for all hMG agents. ² Members should refer to their benefit plan document or certificate of coverage for details regarding benefit coverage for each eligible plan and product.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage and some Oxford Health Plan pharmacy riders contain an explicit exclusion for infertility treatments, including infertility drugs. The member specific benefit plan document must be used to adjudicate infertility benefits.

Some states mandate benefit coverage for infertility treatments, including infertility drugs. These mandates may vary from state to state. Oxford Health Plans follows these mandates, where applicable.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the policy titled [Acquired Rare Disease Drug Therapy Exception Process](#).

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Oxford has engaged Optum to perform reviews of requests for pre-certification (Oxford continues to be responsible for decisions to limit or deny coverage and for appeals). All authorization/pre-certification requests are handled by Optum. To pre-certify a procedure related to the treatment of infertility, please call Optum at 877-512-9340.

This policy refers to the following hMG agent:

- Menopur® (menotropins for injection)

The clinically appropriate dosing for hMG when used in an ART cycle without an FSH product is 450 IU/day or less for not more than 14 days of treatment. The total dose of gonadotropin (hMG and FSH) should not exceed 450 IU per day when used in any mixed stimulation protocol. When used as part of a mixed stimulation protocol (hMG + FSH) or when used alone for ovulation induction or controlled ovarian stimulation the clinically appropriate maximum dosing for hMG agents is 150 IU/day. Exceeding this daily dose and duration of treatment has not been proven to be efficacious in terms of pregnancy outcome.

hMG agents will be referred to as "gonadotropins" in the following medical necessity language.

In absence of a product listed and in addition to applicable criteria outlined within the drug policy, prescribing and dosing information from the package insert is the clinical information used to determine benefit coverage.

The following information pertains to medical necessity review:

General Requirements (applicable to all medical necessity requests): ^{3,4,20,32}

For initial and continuation of therapy, ALL of the following must be met for consideration of treatment:

- Prognosis for conception must be $\geq 5\%$; and
- Adequate ovarian reserve as indicated but not limited to at least **one** the following markers (one or more of the following within the previous 6 months:
 - FSH level < 15 mIU/ml if > 35 years of age; or
 - FSH level < 20 mIU/ml if ≤ 35 years of age; or
 - AMH level > 0.3 ng/ml; or
 - Antral follicle count > 6 ;

- and
- Evidence of adequate ovarian response to stimulation if there has been previously monitored, medicated-stimulated infertility treatment within the previous 6 months. Examples of adequate ovarian response are:
 - One follicle \geq 15 mm diameter for IUI
 - Minimum of 1 follicle \geq 15 mm diameter for ART

Diagnosis-Specific Requirements³²

The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

hMG gonadotropins are proven and medically necessary for:

Ovulation Induction

Gonadotropins are proven and medically necessary for the treatment of ovulatory dysfunction when ONE of the following criteria are met:

- Anovulation; or
- Oligo-ovulation; or
- All** of the following:
 - Amenorrhea; and
 - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; and
 - Failure to ovulate with either Clomid (clomiphene citrate) or Femara (letrozole);
 and
- One** of the following:
 - For assisted reproductive technologies (ART), dose does not exceed 450 IU/day, for no more than 14 days per cycle; or
 - For ovulation induction, dose does not exceed 150 IU/day, for no more than 14 days per cycle.

Gonadotropins are unproven and not medically necessary for the treatment of ovulatory dysfunction in the following situations:

- Beyond the 6th gonadotropin induced ovulatory cycle.
- When there are \geq 4 follicles which are \geq 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment (e.g., doses of gonadotropin down to 37.5 IU per day).
- When used alone for individuals with unexplained infertility.
- When there is a failure to respond to ovulation stimulation (e.g., doses of gonadotropins up to 225 IU per day and no follicles \geq 15 mm in diameter).
- In lieu of clomiphene or letrozole to correct a thin endometrial lining.²⁸⁻³⁰
- An estradiol level $<$ 100 pg/ml/follicle \geq 15 mm in diameter.
- Doses that exceed 450 IU/day for ART or 150 IU/day for ovulation induction, respectively.
- Duration of therapy that exceeds 14 days per cycle.

Controlled Ovarian Stimulation

Gonadotropins are proven and medically necessary for the treatment of controlled ovarian stimulation when ALL of the following criteria are met:

- Used alone or in conjunction with intrauterine insemination; and
- One** of the following:
 - Treatment in individuals with diminished ovarian reserve that have not responded to clomiphene or letrozole; or
 - Initial treatment for individuals with diminished ovarian reserve; or
 - Initial treatment for individuals \geq 40 years of age; or
 - In the setting of unilateral tubal disease when there is no evidence of tubal compromise on the patent side when at least 2 cycles of oral agents (clomiphene or letrozole) have failed to yield a dominant follicle on the side with a patent fallopian tube;
 and
- One** of the following:
 - For assisted reproductive technologies (ART), total gonadotropin dose does not exceed 450 IU/day, for no more than 14 days per cycle; or
 - For controlled ovulation stimulation, dose does not exceed 150 IU/day, for no more than 14 days per cycle.

Gonadotropins are unproven and not medically necessary for the treatment of controlled ovarian stimulation in the following situations:³²

- Treatment in individuals with unexplained infertility, endometriosis, bilateral tubal factor infertility, recurrent pregnancy loss, male factor infertility.^{19,20}

- In lieu of clomiphene or letrozole to correct a thin endometrial lining.²⁸⁻³¹
- When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 225 IU per day and no follicles ≥ 15 mm in diameter).
- An estradiol level <100 pg/ml/follicle ≥ 15 mm in diameter.
- When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment.
- Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.
- Doses that exceed 450 IU/day for ART or 150 IU/day for controlled ovulation stimulation, respectively.
- Duration of therapy that exceeds 14 days per cycle.
- Beyond 4 cycles for individuals age <38 , 2 cycles for individuals age 38-39, and 1 cycle for individuals age 40 and older in the setting ovarian stimulation for diminished ovarian reserve.
- In the setting of very poor/futile prognosis, defined as a FSH level ≥ 15 mIU/ml if ≥ 40 years of age or FSH level ≥ 20 mIU/ml if <40 years of age.

Hypogonadotropic Hypogonadism

Gonadotropins are proven and medically necessary for the treatment of hypogonadotropic hypogonadism when ALL of the following criteria are met:

- **One** of the following:
 - Diagnosis of primary hypogonadotropic hypogonadism; or
 - Diagnosis of secondary hypogonadotropic hypogonadism;
 and
- For the induction of spermatogenesis; and
- Infertility is not due to primary testicular failure.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Menopur[®] is a preparation of gonadotropins (FSH and LH activity), extracted from the urine of postmenopausal women, which has undergone additional steps for purification.

Menopur[®] is a sterile, lyophilized powder intended for subcutaneous (SC) injection after reconstitution with sterile 0.9% Sodium Chloride Injection, USP. Each vial of Menopur[®] contains 75 International Units of follicle-stimulating hormone (FSH) activity and 75 International Units of luteinizing hormone (LH) activity, plus 21 mg lactose monohydrate and 0.005 mg Polysorbate 20 and Sodium Phosphate Buffer (Sodium Phosphate Dibasic, Heptahydrate and Phosphoric Acid). The biological activity of Menopur[®] is determined using the bioassays for FSH (ovarian weight gain assay in female rats) and LH (seminal vesicle weight gain assay in male rats), modified to increase the accuracy and reproducibility of these assays. The FSH and LH activity assays are standardized using the Fourth International Standard for Urinary FSH and Urinary LH, November 2000, by the Expert Committee on Biological Standardization of the World Health Organization (WHO ECBS). Both FSH and LH are glycoproteins that are acidic and water soluble. Human Chorionic Gonadotropin (hCG) is detected in Menopur[®].

Menopur[®], administered for 7 to 20 days, produces ovarian follicular growth and maturation in women who do not have primary ovarian failure. Treatment with Menopur[®] in most instances results only in follicular growth and maturation. When sufficient follicular maturation has occurred, hCG must be given to induce ovulation.

Human menopausal gonadotropin (hMG) is also used for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.²⁶

The American Society for Reproductive Medicine (ASRM) defines infertility as a disease*, defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years. It affects about 10% to 15% of couples.^{2,22}

In addition to age, other factors that influence fertility include lifestyle (smoking, alcohol, caffeine, drugs, and body mass index) and the timing and frequency of intercourse. Normal sperm can survive at least 3 days, but an oocyte can be fertilized for only 12 to 24 hours.

The major causes of infertility include tubal and peritoneal pathology (30% - 40%), ovulatory dysfunction (15%), and male factor (30% - 40%). Uterine and cervical factors are uncommon. Patients without an identifiable cause are classified as unexplained infertility (10%).

Human menopausal gonadotropin (hMG) is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells. In women, the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity.

hMG therapy is used for the development of more eggs when participating in an assisted reproductive technology (ART) program, such as in vitro fertilization.

(*ASRM cites a definition of the term "disease" provided by Dorland's Illustrated Medical Dictionary, 31st edition, 2007:535: "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown.")

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
S0122	Injection, menotropins, 75 IU
S4042	Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle

ICD-10 Diagnosis Code	Description
E28.39	Other primary ovarian failure
E28.8	Other ovarian dysfunction
E29.1	Testicular hypofunction
N91.0	Primary amenorrhea
N91.1	Secondary amenorrhea
N91.2	Amenorrhea, unspecified
N97.0	Female infertility associated with anovulation

CLINICAL EVIDENCE

Proven/Medically Necessary

The Menopur in GnRH Antagonist Cycles with Single Embryo Transfer (MEGASET) study compared the efficacy and safety of highly purified menopausal gonadotropin (hMG) and recombinant follicle stimulating hormone (rFSH) for controlled ovarian stimulation in gonadotropin releasing hormone (GnRH) antagonist cycle with compulsory single-blastocyst transfer was examined in a multicenter, randomized, open-label, assessor-blind, parallel-group, noninferiority trial.²² The trial recruited 810 and randomized 749 women aged 21 to 34 years with a BMI of 18 to 25 kg/m² with a primary diagnosis of infertility being unexplained infertility or mild male factor, among additional inclusion criteria. Women were recruited through 25 infertility centers in seven countries. On day 2 to 3 of the menstrual cycle, patients were randomized in a 1:1 ratio to treatment with hMG (Menopur, n = 374) or rFSH (follitropin beta; Puregon, n = 375). Starting doses for each gonadotropin was fixed at 150 IU for the first 5 days. From stimulation day 6 and on, dosing could be changed by 75 IU per adjustment and no more frequently than every 4 days and a maximum dose of 375 IU daily for a maximum of 20 days. Ganirelix acetate (Orgalutran) was initiated on day 6 as well, 0.25mg daily, and continued through the stimulation period. A single injection of 250 mcg human chorionic gonadotropin (hCG) (choriogonadotropin alpha, Ovitrelle) was injected to induce final follicular maturation when 3 follicles of ≥ 17 mm were observed. The target for ovarian stimulation was to obtain 8 to 10 oocytes. The cycle was cancelled in case of fewer than three follicles with a diameter ≥ 12 mm on day 14 of stimulation or more than 25 follicles with a diameter of ≥ 10 mm. Luteal phase support treatment was with vaginal progesterone capsules (600mg/day) from the day after oocyte retrieval to day 13 to 15 after embryo transfer. The primary endpoint was ongoing pregnancy rate, live birth weights, as well as pharmacodynamic parameters. Noninferiority was to be documented for both the intention-to-treat (ITT) population (all randomized and exposed patients, n = 749), and the per-protocol (PP) population (all randomized and exposed, except those excluded due to protocol violations, n = 676). The PP population included 676 patients (343 for hMG and 333 for rFSH). After 5 days of stimulation, serum FSH concentration was significantly higher ($p < 0.001$) in the hMG group than the rFSH group, and more follicles ≥ 12 mm ($p = 0.011$) as well as higher levels of serum estrogen ($p = 0.003$) and inhibin B ($p < 0.001$) detected on day 6 of

stimulation in the rFSH group than the hMG group. Mean levels of progesterone on day 6 were higher with rFSH ($p=0.25$) than with hMG. At the end of stimulation, no significant differences between groups were noted in the number of follicles ≥ 17 mm or 15 to 16 mm, but significantly ($p=0.24$) more follicles with a diameter of 12 to 14 mm were observed in the rFSH group. Serum concentrations of FSH, LH, and estrogen at the end of stimulation were significantly higher ($p<0.001$) in the hMG group. For 97% of the treatment population oocyte retrieval was performed. Excessive response caused cancellation of therapy in only two rFSH patients and none in the hMG group. The number of oocytes retrieved was significantly higher ($p<0.001$) in the rFSH group, but no significant differences between groups in the percentage of metaphase II oocytes or fertilization rate. Significantly ($p=0.005$) more embryos on day 3 in the rFSH group, but the number of blastocysts on day 5 were not significantly different between groups. Both groups had similar cleavage rate, embryo quality on day 3, blastocyst quality on day 5, and percentage of patients with blastocysts on day 5 (82% hMG and 85% rFSH), and patients with at least one surplus frozen blastocyst (55% and 57%, respectively). Embryo transfer was performed for 82% and 84% of the hMG group and rFSH group patients, respectively. The ongoing pregnancy rate per started cycle was 30% with hMG and 27% with rFSH for the PP population and 29% and 27% respectively, for the ITT population. The treatment difference in ongoing pregnancy rates was 3.0% (95% CI -3.8 to 9.8) and 2.2% (95% CI -4.2 to 8.6) for the PP and ITT populations, respectively, both in favor of hMG. The lower limit of the 95% CI for this difference was well above the pre-established noninferiority margin of -10% for both the PP and ITT populations. The live birth rate after the fresh cycle was 29% with hMG and 26% with rFSH for PP and 28% and 26%, respectively, for the ITT populations. A total of 116 patients (31%) in the hMG group and 122 (33%) in the rFSH group had blastocysts thawed, of whom 107 (29%) and 115 (31%), respectively, had blastocyst transfer in a frozen cycle. The 1 year cumulative ongoing pregnancy rate per patient was 41% for hMG and 39% rFSH for PP population and 40% and 39%, respectively, for the ITT population. The cumulative live birth rate was 40% after hMG and 38% after rFSH for both PP and ITT populations. The overall incidence of adverse events during the fresh cycle was similar for the two treatments, with 39% in the hMG group and 37% in the rFSH group with at least 1 adverse event. OHSS was experienced by 3% (10 patients) in each treatment group. Overall the MEGASET trial establishes evidence that hMG is at least as effective as rFSH in GnRH antagonist cycles with compulsory single-blastocyst transfer.

A multicenter, randomized, open-label, parallel group study compared the efficacy and safety of subcutaneous (SC) and intramuscular (IM) Repronex (menotropins for injection) and Pergonal (menotropins for injection) IM in patients undergoing ovulation induction.²³ 115 infertile, premenopausal, anovulatory, or oligo-ovulatory, nonsmoking women between 18 and 30 years of age, with a BMI < 38 , were recruited from 10 academic and private infertility clinics. Patients meeting inclusion criteria underwent pituitary down-regulation with leuprolide acetate 1 mg/d SC, continued unchanged until the day prior to hCG was administered. Patients who were unsuccessful with down-regulation were removed from the trial. Patients were then randomized into one of three treatment groups: Repronex SC ($n=36$), Repronex IM ($n=36$), or Pergonal IM ($n=36$), 450 IU day 1, then 225 IU daily for the next 4 days. The protocol was amended to 150 IU daily for the first 5 days, followed by individualized daily dosing (max 12 days total), after 4 of the first 6 patients experienced high day 5 estrogen levels and/or excessive multifollicular development. At day 6, investigators adjusted the daily dose upward by 75 to 150 IU (no more frequent than every other day) to a maximum daily dose of 450 IU. When patients had at least one follicle with a mean diameter of ≥ 14 mm and appropriate estrogen levels, a single dose of 10,000 USP units of hCG was administered. Patients who did not have adequate follicular growth or appropriate serum estrogen levels after 12 days of stimulation were considered treatment failures and did not receive hCG and therapy was cancelled. Therapy was also cancelled if the patient was at risk for OHSS or high orders multiple gestations. After hCG administration, patients were instructed on timed intercourse or IUI was performed. Progesterone vaginal gel was permitted for luteal phase support.

Soical et al., compared the efficacy and safety of Repronex SC, IM and Pergonal IM in patient undergoing in vitro fertilization (IVF) in a multicenter, randomized, open-label, parallel-group study.²⁴ The trial recruited 189 premenopausal women with regular ovulatory menstrual cycles undergoing IVF for infertility attributable to tubal factors, endometriosis (stage I or II), or unknown factors. Qualifying patients received leuprolide acetate, 1mg SC daily beginning 7 days before the anticipated onset of menses and continued until the day before hCG was administered and serum estrogen levels were appropriate. If menses did not occur within 20 days after beginning leuprolide treatment or serum estrogen levels were not ≤ 40 pg/mL, then the treatment was stopped. Three patients did not meet criteria to continue the trial. Patients ($n = 186$) were then randomized to receive either Repronex SC or IM (225 IU daily, $n = 60$ or $n = 65$, respectively) or Pergonal IM (225 IU daily, $n = 61$) for 5 consecutive days. Menotropin response was reassessed on day 6, where, based on follicle size and serum estrogen levels, the investigators adjusted the doses, investigators then adjusted the doses upward by 75 to 150 IU/day, no more frequently than every other day with a maximum dose of 450 IU of FSH/day. If there was clinically significant rise in serum estrogen appropriate for the size of the follicles, the dose was kept constant. Menotropin therapy was continued for no more than 12 days, but stopped if estrogen levels were excess of 6,000 pg/mL or if there was a moderate to severe risk for OHSS. On or before day 12 of menotropin therapy, patients meeting specific criteria (follicles ≥ 16 mm, appropriate estrogen levels) were administered hCG (10,000 USP units IM) on the day after the last dose of menotropin. Of 186 patients, 14 (7.5%) did not receive hCG and discontinued treatment. Ultimately, 55 Repronex SC, 61 Repronex IM, and 56 Pergonal IM patients received hCG. After oocyte retrieval and fertilization, a

maximum of four embryos were permitted to be transferred. Beginning on the day of transfer, progesterone (50mg IM daily) was administered for luteal support until either a negative pregnancy test or fetal heart motion in an intrauterine pregnancy was observed. Of the main outcome measures, there was no difference between all treatment groups for the mean number of oocytes retrieved, chemical and clinical pregnancies, incidence of oocyte retrieval and embryo transfer, and peak serum estrogen concentrations. The only significant difference among treatment groups was there was a higher percentage of continuing pregnancies in the Repronex SC group (n = 28; p = 0.46) than in the Pergonal IM group (n = 19). As a secondary measure, fecundity rates were significantly greater for Repronex SC (35.3%) than for either Repronex IM (22.2%; p = 0.008) or Pergonal IM (25.0%; p = 0.043). Multiple birth rates were comparable among the treatment groups. Overall menotropin therapy was well tolerated in all three treatment groups. The only statistically significant difference in adverse events was in the Repronex SC group for a higher incidence of injection site edema (p < 0.02). The authors concluded that Repronex SC is comparable in therapeutic effectiveness and safety to Repronex IM and Pergonal IM in patients undergoing IVF and provides an alternative route of injection for self-administration of gonadotropin.

A multicenter, multinational, randomized, open-label, assessor-blind, parallel-group, non-inferiority study compared high potency human menopausal gonadotropin (hMG, Menopur®) and recombinant follicle stimulating hormone (rFSH, Gonal-F) with respect to the primary endpoint of ovulation induction rate after one cycle of gonadotropin treatment with a low-dose step-up protocol.¹⁶ 184 anovulatory WHO Group II women resistant to clomiphene citrate were included in the study. 91 were randomized to receive hMG and 93 were to receive rFSH. Gonadotropin stimulation was started 2 to 5 days after spontaneous or progesterone-induced menses. The starting dose for each agent was 75 IU daily for 7 days. After the first 7 days, the dose was evaluated according to individual response. The dose was maintained at 75 IU if one follicle was ≥ 10 mm, and increased by 37.5 IU if there were no follicles ≥ 10 mm. The dose could be maintained or adjusted every 7 day period (maximum 225 IU), according to the study protocol, for a maximum duration of 6 weeks. Stimulation continued until the subject met criteria for hCG administration (one follicle ≥ 17 mm or 2 to 3 follicles ≥ 15 mm). Subjects meeting hCG criteria received 5,000 IU hCG subcutaneously to trigger ovulation. Subjects then underwent IUI or had sexual intercourse. The ovulation rate for the per-protocol (PP) population was 85.7% for the hMG group and 85.5% for the rFSH group. For the intent-to-treat population (ITT), the ovulation rate was 83.5% and 84.9% for the hMG and rFSH groups, respectively. Non-inferiority of hMG versus rFSH with respect to ovulation rate was demonstrated with a margin of -11.0% and -12.0% for the PP and ITT populations, respectively. In the ITT population, subjects in the hMG group had on average significantly fewer intermediate-sized follicles (12 – 16 mm) after stimulation versus the rFSH group (1.04 and 1.91, respectively, p = 0.009), but no difference between groups in the mean number of follicles ≥ 17 mm. Development of a single dominant follicle was achieved for 63.7% in the hMG group versus 54.8% group. There were no statistically significant differences between the hMG and rFSH groups with respect to duration, dose, or threshold of gonadotropin dose. The median treatment duration was 13 days in the hMG group versus 11 days in the rFSH group. The median threshold dose was 75 IU in both groups. There was no significant difference in the number or rate of OHSS or cycle cancellation (2.2% with hMG and 9.8% rFSH, p= 0.058). Treatment outcomes of clinical and ongoing pregnancy rates were also similar between groups. The live birth rate was 14.3% and 15.1% with the hMG and rFSH groups, respectively. The frequency of adverse events was similar in the two treatment groups (41.3% hMG and 40.2% rFSH) with a similar adverse event profile. The authors concluded that gonadotropin stimulation with hMG is at least as efficacious as rFSH in anovulatory WHO Group II women resistant to clomiphene citrate.

Technical Assessments

A 2011 Cochrane review was published which compared the effectiveness of recombinant FSH (rFSH) with the three main types of urinary gonadotropins (hMG, purified FSH, and highly purified FSH) for ovarian stimulation in women undergoing IVF and ICSI treatment cycles.²⁵ With the analysis of 42 trials with a total of 9,606 couples, the authors concluded that:

- Comparing rFSH to all other gonadotropins combined, irrespective of down-regulation protocol used, did not result in any evidence of a statistically significant difference in live birth rate (28 trials, 7,339 couples, odds ratio (OR) 0.97, 95% CI 0.87 to 1.08).
 - Suggests that for a group with a 25% live birth rate using urinary gonadotropins, the rate would be between 22.5% and 26.5% using rFSH.
- Comparing rFSH to all other gonadotropins combined, there was no evidence of a difference in the OHSS rate (32 trials, 7,740 couples, OR 1.18, 95% CI 0.86 to 1.61).
 - Suggests that for a group with a 2% risk of OHSS using urinary gonadotropins, the risk would be between 1.7% and 3.2% with rFSH.
- When considering different urinary gonadotropins separately, there were significantly fewer live births after rFSH than hMG (11 trials, N=3,197, OR 0.84, 95% CI 0.72 to 0.99).
 - Suggests that for a live birth rate of 25% using HMG, use of rFSH instead would be expected to result in a rate between 19% and 25%.
- No evidence of a difference in live births when rFSH was compared with purified FSH (5 trials, N=1,430, OR 1.26, 95% CI 0.96 to 1.64) or compared to highly purified FSH (13 trials, N=2,712, OR 1.03, 95% IC 0.86 to 1.22).

- All available gonadotropins are equally effective and safe. The choice of product will depend on the availability, convenience, and associated costs.

Hypogonadotropic Hypogonadism

A prospective, open-label, intent to treat study of 21 men, with a diagnosis of hypogonadotropic hypogonadism, evaluated the efficacy of gonadotropin treatment in stimulating spermatogenesis.²⁶ Six of the 21 men had normal puberty, followed by the onset of hypogonadism, 2 of which had previously fathered children. The 15 remaining men failed to undergo normal pubertal development, 7 of which had cryptorchidism and treated by orchiopexy in childhood. Fourteen normal men were recruited for pretreatment gonadal comparison to the study group, but were not subsequently treated. Study participants were initially treated with human chorionic gonadotropin (hCG) 2,000 IU every Monday, Wednesday, and Friday, which produced normal serum testosterone levels within two months in 18 of the patients. One subject required 4,000 IU, another 5,000 IU, and a third only required 1,250 IU of hCG at the same frequency. If the sperm count did not increase to within the lower limit for normal men (≥ 43 million per ejaculate) after the serum testosterone was normal for six months, the men were started on human menopausal gonadotropins (hMG). The dose given was 75 IU every Monday, Wednesday, and Friday, for the first 4 months and 150 IU at the same frequency for the following four months. Prior to the study, all men had low testosterone levels and only two men had any detectable sperm count. Five patients had normal follicle-stimulating hormone (FSH). During hCG treatment phase, The total sperm count increased to within the normal range in all 6 patients in whom hypogonadism had occurred after puberty, but only 1 in 15 in whom it had occurred before puberty ($p < 0.002$). hMG was then added with 14 patients whom sperm counts did not respond to hCG alone, but whose serum testosterone remained normal. The sperm count increased to within normal limits in 5 of the 7 men with prepubertal onset of hypogonadism but not history of cryptorchidism, but only 1 of 7 men with prepubertal onset of hypogonadism and history of cryptorchidism. The mean maximum sperm count of the 13 men whose counts were within the normal range, treated with hMG, was 86 million, less than the mean of the 14 normal men (154 million). Of the 13 men whose sperm counts became normal, 8 of them were able to conceive, 6 during the protocol period, 2 during an extension period. Only 1 patient was able to conceive whose sperm count did not reach the normal range. In all, 14 pregnancies occurred in nine wives. All patients except one had maximal sperm counts in proximity to the time they conceived. Five other men who achieved normal sperm counts did not conceive. Four did not continue the treatment regimen after the study and one patient's wife refuse evaluation. The authors conclude that hMG treatment will usually increase sperm count to normal in men with hypogonadotropic hypogonadism, unless cryptorchidism has occurred. The need for hMG treatment depends on the time of onset of hypogonadism.

Professional Societies

European Association of Urology

In 2012, the European Association of Urology published guidelines for male infertility.²⁷ These guidelines included the treatment recommendations for hypogonadotropic hypogonadism. The guidelines state that hypogonadotropic hypogonadism can be treated medically. The standard treatment is hCG, with the later addition of hMG or recombinant FSH, depending on initial testicular volume. In some cases of idiopathic hypogonadotropic hypogonadism, spontaneous reversibility of reproductive function has been observed.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
07/01/2018	<ul style="list-style-type: none">• Updated supporting information to reflect the most current references; no change to coverage rationale or lists of applicable codes• Archived previous policy version PHARMACY 288.3 T2