



# CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Policy Number ..... 5019

Subject Lutropin Alfa (Luveris®)

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

## Coverage Policy

**Note: Injectable fertility medications are specifically excluded under most benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.**

If coverage is available for injectable fertility medications, then:

**CIGNA covers lutropin alfa (Luveris®) as medically necessary when BOTH of the following criteria are met:**

- use in combination with human follicle-stimulating hormone (follitropin alfa, Gonal-f®) for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women
- in patients with a profound luteinizing hormone (LH) deficiency defined as LH < 1.2 international units/L.

## General Background

### FDA Approved Indications

Luveris® (lutropin alfa for injection), concomitantly administered with Gonal-f® (follitropin alfa for injection), is indicated for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L). A definitive effect on pregnancy in this population has not been

demonstrated. The safety and effectiveness of concomitant administration of Luveris® with any other preparation of recombinant human FSH or urinary human FSH is unknown.

### **FDA Recommended Dosing**

It is recommended that 75 IU Luveris® be concomitantly administered subcutaneously with 75 IU to 150 IU Gonal-f® as two separate injections in the initial treatment cycle. Concomitant administration of Luveris® with Gonal-f® was studied in the clinical trials for Luveris®. The safety and effectiveness of concomitant administration of Luveris® with any other preparation of recombinant human FSH or urinary human FSH is unknown. Luveris® and Gonal-f® should be administered daily until adequate follicular development is indicated by ovary ultrasonography and serum estradiol. Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) should be given one day after the last dose of Luveris® and Gonal-f®. Treatment with hCG should be withheld if the ovaries are abnormally enlarged or if excessive estradiol production has occurred. If the ovaries are abnormally enlarged or abdominal pain occurs, treatment with Luveris® and Gonal-f® should be discontinued and hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chances of developing Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chances of multiple gestation. A follow-up visit should be conducted in the luteal phase. Doses administered in subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses of Gonal-f® greater than 225 IU per day are not routinely recommended. As in the initial cycle, hCG must be given to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of developing Ovarian Hyperstimulation Syndrome. The couple should be encouraged to have intercourse daily, beginning on the day prior to hCG administration until ovulation becomes apparent in the indices used for the determination of progestational activity.

Lutropin alfa is recombinant human luteinizing hormone (rhLH) indicated for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with a profound luteinizing hormone (LH) deficiency defined as  $LH < 1.2$  international units/L. Lutropin alfa is given concomitantly with recombinant human follicle-stimulating hormone (follitropin alfa, Gonal-f®). Lutropin alfa is classified as a gonadotropin, but is the first gonadotropin to contain only rhLH.

In the ovaries during the follicular phase, LH binds rapidly and reversibly to theca cell receptors and stimulates androgens, which act as substrates for the granulosa cell aromatase enzyme to produce estradiol. While follicle-stimulating hormone (FSH) alone can produce follicular growth, LH is needed for steroid biosynthesis and adequate follicular function and maturation. When given subcutaneously or intramuscularly, lutropin alfa follows a one-compartment pharmacokinetic model and has a terminal half-life of about 18 hours. The steady-state volume of distribution is near 10 liters, and the mean residence time is six hours, indicating a low risk of drug accumulation during daily use. Following subcutaneous administration, lutropin alfa is eliminated with a total body clearance of 2–3 L/h with less than 5% of the drug being excreted unchanged renally.

Six clinical trials have studied lutropin alfa in women classified as being infertile due to hypogonadotropic hypogonadism. Of the six clinical trials, three were placebo-controlled trials, two were observational studies, and one was a pilot study to determine if there is a ceiling effect of LH. Three studies are available as abstracts only. All study participants were premenopausal adult women of normal body mass index, thyroid function, and serum prolactin and testosterone levels. Another factor common to study participants was the presence of LH deficiency.

The primary endpoint in most of the trials is follicular development, defined as:

- at least one follicle with a diameter  $\geq 17$  or 18 mm
- a preovulatory serum estradiol (E2) peak level ( $\geq 400$  to 587 pmol/L)
- a mid-luteal serum progesterone (P4) peak level ( $\geq 25$  to 32 nmol/L)

To complete follicular development and induce ovulation in the absence of an endogenous LH surge, a single dose of human chorionic gonadotropin (hCG) 5,000–10,000 international units is administered after the treatment period. If ovarian hyperstimulation or excessive estradiol production occurred, hCG was not given.

The European Recombinant Human LH Study Group conducted a randomized, dose-finding study in 38 women throughout Europe. All women received rhFSH 150 international units plus either 0, 25, 75, or 225 international units daily of lutropin alfa subcutaneously for up to 14 days, with the possibility of repeating for two additional cycles. This study was one of a few pivotal studies Serono, Inc. used to obtain U.S. Food and Drug Administration (FDA) approval. As a result, the FDA carefully analyzed the statistics and concluded their own results. The sponsor analysis revealed that 11% in the no therapy group, 25% in the 25 international units group, 64% in the 75 international units group, and 70% in the 225 international units group achieved follicular development ( $p=0.0044$ ). The FDA analysis revealed 11%, 25%, 45%, and 40%, respectively ( $p=0.157$ ) and concluded there was no difference between the groups. There were five people at risk for ovarian hyperstimulation syndrome (OHSS), and they did not receive hCG. The study authors included these people at risk for OHSS as successes, but the FDA considered these subjects failures; hence, the differences between the two analyses. There was no difference between the groups in terms of adverse events. Overall, the authors concluded that 75 international units daily is the minimum effective dose of lutropin alfa to obtain follicular development.

A second dose-finding study was conducted in the United States by O'Dea and colleagues and is available as an abstract only. A major difference in this study to the European study is that the inclusion criteria were not as strict, with LH  $\leq 13.3$  international units/L and FSH  $\leq 11$  international units/L being required. Forty women were given the same medication regimen as the European dose-finding study, and again the FDA performed their own analysis of the data. The sponsors reported that 64% in the no therapy group, 100% in the 25 international units group, 73% in the 75 international units group, and 67% in the 225 international units group achieved follicular development ( $p=0.774$ ). The FDA analysis revealed 45%, 78%, 64%, and 67%, respectively, ( $p=0.67$ ), and agreed with the sponsors that the use of lutropin alfa with rhFSH did not result in a statistically significant benefit for follicular development. When the subjects with a serum LH  $\leq 1.2$  international units/L were analyzed separately, a statistically significant dose-related benefit was seen with response rates of 0%, 100%, 66.7%, and 75%, respectively ( $p=0.039$ ). These results are important because they confirm the need for lutropin alfa supplementation in women with profound LH deficiency, but it is unclear whether the authors included women at risk for OHSS as successes or failures. If they included them as successes, the above percentages may overestimate the benefit. The assessment of adverse events concluded that 84.4% of those treated with lutropin alfa in combination with rhFSH compared to 65% of those treated with rhFSH alone experienced side effects, but the adverse events were mostly mild to moderate in severity. There was no discussion of OHSS or mention of any subjects who were at risk for developing OHSS.

Based on these two dose-finding studies, the dose of 75 international units was chosen as the lowest effective dose. The European study seems to confirm this decision, but the United States study shows higher response rates in the 25 international units group, both when all subjects were analyzed and when a subgroup of subjects was analyzed. Although perhaps not statistically significantly superior, the 25 international units dose may, in fact, be the lowest effective dose. The FDA expressed this concern and requested that a larger dose-finding study be completed to address this issue. Three efficacy studies used 75 international units as the treatment dose.

A third study in which the FDA analyzed the data was conducted by The Study 21008 Investigator Group. This study is available as an abstract only. The aim of this study was to confirm the dose of 75 international units as the lowest effective dose and to further define the efficacy and safety of lutropin alfa in combination with rhFSH. Thirty-nine women were enrolled in this double-blind, placebo-controlled trial and were randomized to either rhFSH 150 international units plus placebo or rhFSH 150 international units plus lutropin alfa 75 international units. The sponsor analysis revealed that 15.4% in the placebo group and 65.4% in the treatment group had follicular development ( $p=0.006$ ), compared to the 8% vs. 38% in the FDA analysis ( $p=0.063$ ). Adverse events were reported by 33.3% of patients in both groups. One placebo patient experienced severe OHSS. The authors concluded that this population of women with profound LH and FSH deficiency required supplementation with lutropin alfa and that the results supported the efficacy and safety of lutropin alfa demonstrated in the dose-finding studies.

O'Dea and colleagues conducted an open-label descriptive study in 31 women who had been subjects in study 21008. This study is available as an abstract only. All subjects received lutropin alfa 75 international units as a fixed dose and rhFSH 75–225 international units as a flexible dose based on individual response. Overall, 16 of 31 subjects achieved follicular response (51.6%). Because this was an extension study, very few subjects were

LH-naïve. Of the 11 who were, six achieved follicular development (54%). The study authors assessed clinical pregnancy as a secondary outcome. In the 54 cycles completed, there were 16 clinical pregnancies (29.6%). This included six multiple gestations. While pregnancy is considered a positive outcome, multiple gestation is a negative outcome. Adverse events were experienced by 15 of the 31 patients (48.4%) and were mostly mild or moderate in severity, although one patient was hospitalized for moderate OHSS. The authors concluded that flexible rhFSH dosing with lutropin alfa 75 international units provides good patient response rates. The dose of rhFSH correlated with the most successful follicular development was not discussed in the abstract, so it is difficult to determine exactly the optimal dose of rhFSH. This study did not contain a placebo arm and is unable to give any information on the lowest effective dose. However, this study does support the safe use of lutropin alfa in combination with rhFSH.

Burgues and the Spanish Collaborative Group on Female Hypogonadotropic Hypogonadism conducted an open-label, phase III descriptive study in 38 women. In the first cycle, all subjects received lutropin alfa 75 international units as a fixed dose and rhFSH 150 international units as a flexible dose based on individual response. The subjects were able to repeat for two additional cycles, increasing the dose of lutropin alfa based on response in the first cycle. The analysis of the first cycle revealed 33 of 38 subjects achieved follicular development (86.8%). Considering all cycles, 67 of 84 completed cycles resulted in follicular development (79.8%). These results do not include those women at risk for OHSS as successes. Of the 84 cycles, there were 15 clinical pregnancies reported (17.9%), including four pairs of twins. Nine of the 38 subjects had adverse events (23.7%), which were mostly mild to moderate. There was one patient with mild OHSS and two patients with moderate OHSS. Although the authors did not reveal the actual starting and ending lutropin alfa doses in the subjects achieving follicular response or pregnancy, they did state that, in 94% of the cycles, the dose of lutropin alfa used was 75 international units. This gives further support to the use of 75 international units as an effective dose.

Overall, the primary endpoint of follicular development was met in 38–64% of patients in the placebo trials and 51.6–86.8% of patients in the observational trials. Most women who will respond to lutropin alfa will respond to 75 international units, while a small minority of them may need higher doses. When clinical pregnancy was assessed as a secondary outcome in the observational studies, up to 30% of the completed cycles resulted in pregnancy.

The clinical trials reported an adverse event rate similar to that experienced with recombinant human FSH alone. Most adverse drug reactions were mild to moderate and self-limiting. There is a 6% risk of developing OHSS, but it does not appear that lutropin alfa causes OHSS at a greater rate than other gonadotropins.

No formal drug interaction studies have been conducted with lutropin alfa. Lutropin alfa is contraindicated in women who exhibit any of the following: prior hypersensitivity to human LH preparations or one of their excipients; primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; uncontrolled organic intracranial lesion, such as a pituitary tumor; abnormal uterine bleeding of undetermined origin; ovarian cyst or enlargement of undetermined origin; sex hormone-dependent tumors of the reproductive tract and accessory organs; or pregnancy.

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## Coding/Billing Information

**Note:** This section is currently unavailable.

\*Current Procedural Terminology (CPT®) © 2008 American Medical Association: Chicago, IL.

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## Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	5019	Lutropin Alfa (Luveris®)
Great-West Healthcare	1/2007	P05.103.1	Infertility

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