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About Author

Chengdu Kaijie Biopharm Co, Ltd. (KJBP) is one of leading peptide manufacturers in Asia. With its highest capacity of production in China and the outstanding quality of peptide products, Kaijie holds a unique position.

Gonadorelin

1.Adult Dosage

1.1 Normal Dosage

1.1A Parenteral route)

1.1. A.1 Hypothalamic amenorrhea, Primary

a) Gonadorelin acetate 5 micrograms intravenously every 90 minutes is recommended for primary hypothalamic amenorrhea. This may be administered by using gonadorelin 0.8 milligram/8 milliliters at 50 microliters/pulse in the Lutrepulse Pump(R). Ovulation is induced in approximately 68% of patients with hypothalamic amenorrhea using this regimen. The recommended treatment interval is 21 days. For refractory patients after 3 treatment intervals, the dose may be incrementally increased. When ovulation occurs, the gonadorelin should be continued for two weeks to maintain the corpus luteum.

b) Dosages of intravenous gonadorelin acetate of 1 to 20 micrograms have been used in clinical studies. The Lutrepulse Pump(R) is capable of delivering 2.5, 5, 10, or 20 micrograms of gonadorelin acetate every 90 minutes.

1.1. A.2 Pituitary gonadotropin measurement; Diagnosis

a) The recommended dose for the assessment of hypothalamic-pituitary-gonadotropic function is 100 micrograms gonadorelin hydrochloride administered subcutaneously or intravenously

1.1. B ADMINISTRATION TECHNIQUE

1) HYPOTHALMIC/PITUITARY FUNCTION EVALUATION

a) Patients receiving the gonadorelin hydrochloride test should have venous blood samples drawn 15 minutes before and immediately before gonadorelin hydrochloride administration. A luteinizing hormone baseline level is obtained by averaging these 2 samples. A bolus of 100 micrograms of gonadorelin should be administered subcutaneously or intravenously. Venous blood samples should be drawn at 15, 30, 45, 60, and 120 minutes after administration. Blood samples should be handled as recommended by the laboratory that will determine the luteinizing hormone content. The ultimate value of this test depends on the reliability of the laboratory performing the radioimmunoassay. The results from different laboratories may vary due to inter-assay and intra-assay variability. The single-injection test does not measure pituitary gonadotropic reserve.

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b) Females who are receiving the gonadorelin hydrochloride test and for whom the phase of the menstrual cycle can be established should receive the test in the early follicular phase (days 1 to 7) since the pituitary response to gonadorelin varies during different phases of the menstrual cycle. These changes in pituitary response to gonadorelin stimulation appear to be mediated by the changing concentrations of estradiol-17 beta and progesterone induced by ovarian activity.

c) In cases where there is a borderline response the gonadorelin hydrochloride test should be repeated.

d) Supplied with the manufacturer's package information are luteinizing hormone response curves in normal subjects analyzed from the results of clinical trials by the manufacturer. Luteinizing hormone values are reported in units (mIU/milliliter) versus time in minutes. Individual patient responses should be plotted on the appropriate curve. A subnormal response is defined as 3 or more luteinizing hormone values which fall below the 10th percentile (line B of the normal luteinizing hormone response curve). A representative range of normal baseline luteinizing hormone levels as determined from the literature is as follows:

Source:	**Value:**
Men	5 to 25 mIU/mL
Women	
follicular phase	5 to 25 mIU/mL
midcycle peak	50 to 150 mIU/mL
luteal phase	5 to 25 mIU/mL
postmenopausal	50 to 160 mIU/mL

2) PRIMARY HYPOTHALAMIC AMENORRHEA

a) Gonadorelin acetate should only be administered intravenously with a Lutrepulse Pump(R).

b) Therapy with gonadorelin acetate should be conducted by physicians familiar with pulsatile gonadotropin-releasing hormone delivery and the clinical ramifications of ovulation induction

1.1. C INTRAVENOUS SOLUTION PREPARATION

1) Gonadorelin acetate, both the 0.8-milligram and the 3.2-milligram strengths, should be reconstituted with 8 milliliters of diluent. The saline diluent should be injected onto the lyophile cake and shaken for a few seconds to produce a clear, colorless solution free of particles.

1.2 Dosage in Renal Failure

A) The response to a single 100-microgram intravenous dose of gonadorelin hydrochloride is altered in patients with chronic renal failure as compared with normal subjects. Average pre-treatment and post-treatment serum luteinizing hormone (LH) levels were

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notably higher in patients with chronic renal failure than in those with normal renal function, however, the magnitude of the change in levels was not consistently greater in chronic renal failure patients. Average levels of luteinizing hormone in female patients with normal renal function prior to receiving gonadorelin were 11.3 mIU/milliliters as compared with 27.8 mIU/milliliter in patients with chronic renal failure receiving no hemodialysis. After receiving gonadorelin, levels of luteinizing hormone were 35.4 and 128.9 mIU/milliliter, respectively. In male patients luteinizing hormone levels were 12.4 and 76.1 mIU/milliliter before administration of gonadorelin and were 111.1 and 239.6 mIU/milliliter, respectively, after gonadorelin administration

B) Renal failure, but not hepatic insufficiency, prolonged the half-life of gonadorelin

1.3 Dosage in Hepatic Insufficiency

A) Renal failure, but not hepatic insufficiency, may prolong the half-life of gonadorelin

1.4 Dosage Adjustment During Dialysis

A) Patients with chronic renal failure undergoing hemodialysis appear to respond differently to a single dose of 100 micrograms of gonadorelin hydrochloride than do patients with normal renal function. Luteinizing hormone levels before injection of gonadorelin were 11.3 mIU/milliliters in patients with normal renal function and 72.4 mIU/milliliters in patients undergoing hemodialysis. After receiving 100 micrograms gonadorelin intravenously the levels were 35.4 mIU/milliliter and 240.1 mIU/milliliter, respectively. In male patients luteinizing levels were 12.4 mIU/milliliter and 102.8 mIU/milliliter before gonadorelin administration and 111.1 and 267.1 mIU/milliliter, respectively, after gonadorelin

2. Pharmacokinetics

2.1 Onset and Duration

A) Onset

1) Peak Response

a) Peak levels of luteinizing hormone, intravenous: 13.5 to 25 minutes.

b) Peak levels of luteinizing hormone, subcutaneous: delayed

1) After subcutaneous administration, peak levels are decreased by approximately 75% to 95%. Absorption of gonadorelin after subcutaneous injection may be further impaired by obesity

B) Duration

1) Single Dose

a) Return to baseline luteinizing hormone-releasing hormone level, intravenous: 60 to 90 minutes

1) Time to return to baseline luteinizing hormone- releasing hormone after intravenous injection of gonadorelin is dose dependent. With 1 and 2.5 mcg of gonadorelin injected, the average time to return to baseline is 20.6 and 37.5 minutes

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respectively. With gonadorelin 5 and 20 mcg, the average time to return to baseline exceeded 60 minutes.

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Intravenous: 1.2 to 3 minutes

2.3 Absorption

A) Bioavailability

1) Subcutaneous: reduced from intravenous route by approximately 33%.

2.4 Distribution

A) Distribution Kinetics

1) Distribution Half-Life

a) 2 to 10 minutes

2.5 Metabolism

A) Metabolism Sites and Kinetics

1) Plasma, extensive

B) Metabolites

1) Various peptide fragments, inactive

2.6 Excretion

A) Kidney

1) Renal Clearance (rate)

a) 500 to 1500 L/day

B) Total Body Clearance

1) 455 mL/min/1.86 m(2) (in men); 1769 mL/min/1.86 m(2) (in women)

a) Tamoxifen decreased average clearance rates to 357 and 1558 mL/min/1.86 m(2) for men and women, respectively. The decrease in clearance induced by tamoxifen was significant for men but not for women.

2.7 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 10 to 40 minutes

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