rFSH

Recombinant Human Follicle Stimulating Hormone

Presentation

rFSH consists of a freeze-dried powder for injection and a solvent for reconstitution. The active ingredient is Recombinant Human Follicle Stimulating Hormone which is obtained from the Chinese Hamster ovary cells.

Each vial contains 75 IU Recombinant Human Follicle Stimulating Hormone BP.

Description

rFSH is a Follicle Stimulating Hormone (FSH) preparation of recombinant DNA origin, which consists of two non-covalently linked, nonidentical glycoproteins designated as the α- and β-subunits. The α- and β-subunits have 92 and 111 amino acids respectively, and their primary and tertiary structure are indistinguishable from those of human Follicle Stimulating Hormone. Recombinant FSH production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in bioreactors. Purification by immunochromatography using an antibody specifically binding FSH results in a highly purified preparation with a consistent FSH isoform profile and a high specific activity. The biological activity of rFSH is determined by measuring the increase in ovary weight in female rats. The in vivo biological activity of rFSH has been calibrated against the first International Standard for Recombinant Human Follicle Stimulating Hormone established in 1995 by the Expert Committee on Biological Standards of the World Health Organization. rFSH contains no Luteinizing Hormone (LH) activity.

Therapeutic Class: Gonadotrophin

Pharmacological Properties

rFSH administered for 7 to 12 days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with rFSH in most instances results only in follicular growth and maturation. When sufficient follicular maturation has occurred, HCG must be given to induce ovulation.

Indications

In the Female:

Ovulation Induction

rFSH administered SC with HCG in a sequential manner, which is indicated for ovulation induction in patients who have previously received pituitary suppression.

Multi-follicular Development

During ART

rFSH administered SC in conjunction with HCG is indicated for multiple follicular developments (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

Polycystic Ovarian Syndrome (PCOS)

Used to treat Polycystic Ovarian Syndrome (PCOS) related infertility

In the Male:

Male infertility treatment in combination with HCG Induction of Spermatogenesis in men deficient spermatogenesis due to Hypogonadotrophic-hypogonadism.

Dosage and Administration

To prevent painful injections and minimize leakage from the injection site rFSH should be slowly administered subcutaneously. The subcutaneous injection site should be alternated to prevent lipoathrophy. Any unused solution should be discarded. Subcutaneous injection of rFSH may be carried

out by patient or partner, provided that proper instructions are given by the physician. Self-administration of rFSH should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

Dosage in Female

There are great inter and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set an uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of estradiol levels. There should be consideration to minimize the risk of unwanted ovarian hyperstimulation. rFSH can be given either alone, or in combination with a GnRH analogue to prevent premature luteinisation. In the latter case, especially when using a GnRH agonist, a higher total treatment dose of rFSH may be required to achieve an adequate follicular response. Clinical experience with rFSH is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Ovulation Induction in Women

Starting daily dose of 75 international units (IU) of rFSH is administered subcutaneously/ subcutaneous for at least the first 7 days. The dose is increased by 25 or 75 international units (IU) at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response. When an acceptable pre-ovulatory state is achieved, final oocyte maturation is achieved with 5000 to 10,000 international units (IU) of human chorionic gonadotropin (HCG). The woman and her partner should have intercourse daily, beginning on the day prior to the administration of HCG and until ovulation becomes apparent.

Assisted Reproductive Technology (ART)

In Women, Starting dose of 150 to 300 international units (IU) of rFSH is administered subcutaneous for at least the first 4 days of treatment. Subsequent doses are adjusted based upon ovarian response as determined by ultrasound evaluation of follicular growth and serum estradiol levels. Final oocyte maturation is induced with a dose of 5000- 10,000 international units of HCG Oocyte (egg) retrieval is performed 34 to 36 hours later.

PCOS

rFSH injections are therefore given each morning as a subcutaneous injection. It is best to start with the lowest dose of rFSH per day (using 75 IU per day). These doses are used for 4 to 6 days at a time. The ovarian response is determined by measuring estrogen levels in the blood. When the estrogen begins to rise, the rFSH is successfully growing an egg or eggs. If there is no response to a dose of rFSH in 5- 6 days of injections the dose will be increased. The normal dose increments are 75 units, 100 units, 150 units and 300 units per day. Most patients respond with 75 IU to 150 IU per day. However it is very important that increments are only made cautiously.

Dosage in Male

Induction of Spermatogenesis in Men

Pre-treatment with HCG alone (2500 international units twice weekly) is required. If serum testosterone levels have not normalized after 8 weeks of HCG treatment, the dose may be increased to 5000 international units (IU) twice a week. After normalization of serum testosterone levels, administer 300 international units (IU) per week (300 international units twice weekly or 100 international units three times weekly) of rFSH subcutaneously with the same pre-treatment HCG dose used to normalize testosterone level.

Reconstitution
To prepare the solution, inject 1 ml water for injection into the vial of 75 IU rFSH. Do not shake, but gently swirl until the solution is clear. Generally, rFSH dissolves immediately. Check the liquid in the container; if it is not clear or contains particles, do not use it. For patients requiring a single injection from multiple vials of rFSH up to 3 vials can be reconstituted with 1 ml water for injection. This can be accomplished by reconstituting a single vial as described above. Then draw the entire contents of the first vial into a syringe and inject the contents into a second vial of lyophilized rFSH. Gently swirl the second vial, once again checking to make sure the solution is clear and free of particles. This step can be repeated with 1 additional vial for a total up to 4 vials (300 IU) of 75 IU rFSH.

Adverse Reactions
Recombinant FSH sometimes excites the ovaries too much. This may cause pelvic pain or breathing problems. It may also make you urinate less. In rare cases, patients with this problem have had serious lung problems, including fluid in the lungs, troublebreathing, and worsening of asthma blood clots, Severe Pelvic pain, Chest pain, or Abdominal pain, Nausea, Vomiting, Sudden weight gain, Bloating, Trouble, Breathing. Recombinant FSH may cause twins or multiple births.

Contraindications
n Tumors of the ovary, breast, uterus, pituitary or hypothalamus
n Pregnancy or lactation
n Undiagnosed vaginal bleeding
n Hypersensitivity to the active substance or to any of the excipients
n Primary ovarian failure
n Fibroid tumors of the uterus incompatible with pregnancy
n Primary testicular failure

Special Warnings and Special Precautions for Use

- The presence of uncontrolled non gonodal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) should be excluded.
- In pregnancies occurring after induction of ovulation with gonadotrophin preparations, there is an increased risk of multiple gestations (Multiple birth).
- There has been no reports of hypersensitivity to Recombinant FSH, but there remains the possibility of anaphylactic responses.
- The first injection of Recombinant FSH should be performed under direct medical supervision.
- Since infertile women undergoing assisted reproduction and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
- Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
- Unwanted ovarian hyperstimulation in the treatment of female patients, ultrasonographic assessment of follicular development, and determination of oestradiol levels should be performed prior to treatment and at regular intervals during treatment. Apart from the development of a high number of follicles, oestradiol levels may rise very rapidly, e.g. more than a daily doubling for two or three consecutive days, and possibly reaching excessively high values. The diagnosis of ovarian hyperstimulation may be confirmed by ultrasound examination. If this unwanted ovarian hyperstimulation occurs (i.e. not as part of controlled ovarian hyperstimulation in medically assisted reproduction programs), the administration of Recombinant FSH should be discontinued. In that case pregnancy should be avoided and HCG

must be withheld, because it may induce in addition to multiple ovulation, the Ovarian Hyperstimulation Syndrome (OHSS).
- In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

Pregnancy and Lactation
Category: X (Recombinant FSH must not be used during pregnancy and lactation).

Overdosage
No data on acute toxicity of Recombinant FSH in humans is available, but the acute toxicity of Recombinant FSH and of urinary gonadotrophin preparations in animal studies have been shown to be very low. Too high a dosage of Recombinant FSH may lead to hyperstimulation of the ovaries (see "Unwanted ovarian hyperstimulation").

Pharmaceutical Precautions
- Store at 2oC-8oC (in refrigerator).
- Do not keep in deep freeze.
- Keep out of reach of children.

Commercial Pack
Each pack contains 1 vial of 75 IU Recombinant Human Follicle Stimulating Hormone (rFSH) as Lyophilized Powder with 1 ml Water for Injection, a Sterile Disposable Syringe, one Subcutaneous Needle and one Needle for Reconstitution.