

For the use of a registered medical practitioner or a hospital or a laboratory only

# <sup>Rx</sup>Follitropin beta Recombinant Human Follicular Stimulating Hormone

## FostiRel™

### DESCRIPTION

*FostiRel™* (follitropin beta injection) contains recombinant human follicle stimulating hormone (r-FSH), a glycoprotein hormone which is manufactured by recombinant DNA (rDNA) technology. The active drug substance, follitropin beta, has a dimeric structure containing two glycoprotein subunits (alpha and beta). Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell line that has been transfected with a plasmid containing the two subunit DNA sequences encoding for human follicle stimulating hormone (hFSH). The purification process results in a highly purified preparation with a consistent hFSH isoform profile and high specific activity. The compound is considered to contain no LH activity. The amino acid sequence and tertiary structure of *FostiRel™* are indistinguishable from that of hFSH of urinary source.

*FostiRel™* is presented as a sterile aqueous solution intended for SUBCUTANEOUS administration.

### COMPOSITION

*FostiRel™* contains r-FSH solution for injection in multidose vials and single use pre-filled syringes. The active substance is Follitropin beta (recombinant follicle stimulating hormone, r-FSH), produced by genetic engineering of a Chinese hamster ovary (CHO) cell line. The formulated solution ready for use contains r-FSH corresponding to 750 IU/ml (specific in vivo bioactivity equal to approximately 10000 IU FSH/mg protein) of active protein.

*FostiRel™* is available in multi-dose vials containing either 300 IU of r-FSH in 0.4 ml solution for injection or 900 IU of r-FSH in 1.2 ml solution for injection or 1200 IU of r-FSH in 1.6 ml solution for injection or 2000 IU of r-FSH in 2.7 ml solution for injection.

*FostiRel™* is also available as pre-filled syringe (PFS) for one-time subcutaneous administration in the strength of 75 IU or 150 IU or 225 IU of r-FSH in 0.1, 0.2 and 0.3 ml of solution for injection in 0.5 ml syringe. Other ingredients are sucrose, sodium citrate, polysorbate 20, and L-methionine dissolved in water for injection at neutral pH. Benzyl alcohol is present as preservative in multi dose vials only.

### CLINICAL PHARMACOLOGY

Follicle stimulating hormone (FSH), the active component in *FostiRel™*, is required for normal follicular growth, maturation, and gonadal steroid production. 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. Phase III clinical trials conducted to establish the efficacy and safety of *FostiRel™* have shown it to be inducing ovarian stimulation, within stipulated time, comparable to other products containing r-FSH. *FostiRel™* stimulates ovarian follicular growth in women who do not have primary ovarian failure. The average dose of *FostiRel™* required attain the required ovarian stimulation during Clinical Trial was 2367 IU over a period of 7-14 days. In order to effect the final phase of follicle maturation, resumption of meiosis and rupture of the follicle in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given following treatment with r-FSH when patient monitoring indicates that appropriate follicular development parameters have been reached.

### Pharmacokinetics

The bioavailability of r-FSH following subcutaneous administration is investigated in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. After subcutaneous injection the apparent dose absorbed was 77.8%.

The volume of distribution of r-FSH in healthy, pituitary-suppressed, female subjects following intravenous administration of a 300 IU dose was approximately 8 L.

*FostiRel™* is biochemically very similar to urinary FSH and it is therefore anticipated that it is metabolized in the same manner.

The pharmacokinetics of *FostiRel™* has not been determined in special populations such as geriatric, pediatric, renally impaired, and in patients hepatic impairment.

### INDICATIONS AND USAGE

*FostiRel™* (follitropin beta injection) is indicated for the treatment of female infertility in following clinical situations:

- for development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program.
- in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure, for the induction of ovulation and pregnancy.

*FostiRel™* is also indicated in males with deficiency of spermatogenesis due to hypogonadotrophic hypogonadism.

### Selection of Patients

#### Before treatment with r-FSH is instituted:

1. A thorough gynecologic and endocrinologic evaluation of the patient must be performed. The evaluation should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of reviewing a patient's history, performing a physical examination, determining serum hormonal levels as indicated, and optionally performing an endometrial biopsy. Patients with tubal pathology should receive *FostiRel™* only if enrolled in an ART program.
2. Primary ovarian failure should be excluded by the determination of circulating gonadotropin levels.
3. Careful examination should be made to rule out early pregnancy.
4. Evaluation of the partner's fertility potential should be considered before the workup procedure.

### CONTRAINDICATIONS

*FostiRel™* is contraindicated in patients who have hypersensitivity to the active substance or to any of the excipients.

Besides this, *FostiRel™* is also contraindicated in patients with-

- Tumours of the ovary, breast, uterus, testis, pituitary or hypothalamus.
- Undiagnosed vaginal bleeding.
- Primary ovarian failure.
- Ovarian cysts or enlarged ovaries, not related to polycystic ovarian disease (PCOD).
- Malformations of the sexual organs incompatible with pregnancy.
- Fibroid tumors of the uterus incompatible with pregnancy.
- Primary testicular failure.
- Pregnancy and lactation.

### WARNINGS AND PRECAUTIONS

Before administering *FostiRel™*, the presence of uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) should be excluded.

- In pregnancies occurring after induction of ovulation with gonadotropin preparations, there is an increased risk of multiple gestations. Appropriate rh-FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestations, especially high order, carry an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
- The first injection of *FostiRel™* 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 with r-FSH treatment 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.
- The incidence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
- 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 *FostiRel™* 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). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction that may be accompanied by morphologic changes on liver biopsies have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
- There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the baseline risk of these tumours in infertile women.
- Women with generally recognized risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m<sup>2</sup>) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotropins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
- Elevated endogenous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to r-FSH/hCG therapy.
- In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

### Laboratory Tests

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:

- a. A rise in basal body temperature,
- b. Increase in serum progesterone, and
- c. Menstruation following the shift in basal body temperature.

When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

- a. Fluid in the cul-de-sac,
- b. Follicle showing marked decrease in size, and
- c. Collapsed follicle.

### Carcinogenesis and Mutagenesis

Long-term toxicity studies in animals have not been performed with *FostiRel™* to evaluate the carcinogenic potential of the drug.

### Pregnancy

Pregnancy Category X. There is no indication for use of *FostiRel™* during pregnancy. No teratogenic risk has been reported, following controlled ovarian stimulation using gonadotropins.

### Nursing Mothers

Though it is not known whether *FostiRel™* is excreted in human milk or not, *FostiRel™* should not be used during breast-feeding.

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### Geriatric Use

Clinical studies of Follitropin beta did not include subjects aged 65 and over.

### ADVERSE REACTIONS

Assisted Reproductive Techniques (ART)

Rates of adverse events from other studies of r-FSH in infertile women treated with in vitro fertilization after pituitary suppression with a GnRH agonist are summarized in Table 1.

Table 1. Incidence of Adverse Clinical Experiences (> 1%)

Adverse Event	Incidence
Miscarriage	11.0%
Ovarian Hyperstimulation Syndrome	5.2%
Ectopic pregnancy	3.0%
Abdominal pain	2.5%
Injection site pain	1.7%
Vaginal hemorrhage	1.5%

### Ovulation Induction

Rates of adverse events from other studies of r-FSH in chronic anovulatory women who failed to ovulate and/or conceive during clomiphene citrate treatment are summarized in Table 2.

Table 2. Incidence of Adverse Clinical Experiences (> 1%)

Adverse Event	Incidence
Miscarriage	9.5%
Ovarian Hyperstimulation Syndrome	7.6%
Abdominal discomfort	2.9%
Abdominal pain, lower	2.9%
Abdominal pain	1.9%
Ovarian cyst	2.9%

The following adverse events have been reported in women treated with gonadotropins: pulmonary and vascular complications, hemoperitoneum, adnexal torsion (as a complication of ovarian enlargement), dizziness, tachycardia, dyspnea, tachypnea, febrile reactions, flu-like symptoms including fever, chills, musculoskeletal aches, joint pains, nausea, headache and malaise, breast tenderness, and dermatological symptoms (dry skin, erythema, body rash, hair loss, and hives)

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

The Phase III studies conducted with *FostiRel™* to assess the efficacy and safety, no patient reported any adverse reaction.

### Effects on ability to drive and use machines

*FostiRel™* has no or negligible influence on the ability to drive or use machines.

### Congenital Anomalies

The incidence of congenital malformations after ARTs may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, sperm characteristics) and to the higher incidence of multiple gestations after ART. There are no indications that the use of gonadotropins during ART is associated with an increased risk of congenital malformations.

### OVERDOSAGE

There is no data available on acute toxicity of *FostiRel™* in humans. High dose ( 8 to 16 times the human clinical dose) acute toxicity studies in rats and mice by subcutaneous route using *FostiRel™* has revealed no adverse effects.

Too high dose of *FostiRel™*, if given inadvertently, can lead to ovarian hyperstimulation.

### DOSAGE AND ADMINISTRATION

#### Dosage in females

– for development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program:

The dosage regimen may vary according to the physician's preference and the patient's response. In general, stimulation of follicular growth is achieved by starting with daily administration of 150 to 225 IU *FostiRel™* by subcutaneous route for a period of 4 days. Thereafter, the dose may be adjusted according to the individual's ovarian response.

Maturation of follicles is monitored by pelvic ultrasonography and measurement of plasma estrogen levels. In responding patients, daily maintenance doses of 75 to 300 IU for 6 to 12 days are usually sufficient, although longer treatment may be necessary. The maximum individualized daily dose safely used in various clinical studies was 450 IU. There is limited experience with higher doses, though use of up to 900 IU daily dose has also been reported in literature. When ultrasonic evaluation indicates the presence of at least 3 follicles of sufficient size and there is evidence of a good estradiol response, the final phase of maturation of the follicles is induced by administration of hCG given 30 to 40 hours after the last administration of follitropin beta in a dose of 5000 to 10000 IU. After embryo transfer, up to 3 repeat injections of 1000 to 3000 IU hCG each may be given within the following 9 days to provide luteal phase support.

*FostiRel™* may be given alone, or in combination with clomiphene citrate to stimulate the endogenous production of gonadotropins, (see Precautions, Drug Interactions) or in combination with a GnRH agonist to prevent premature luteinization.

– in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure, for the induction of ovulation and pregnancy:

The dosage of *FostiRel™* required to produce follicular maturation must be individualized according to ovarian response. The growth and development of follicles, timing of hCG administration, detection of ovarian enlargement and minimization of the risk of OHSS and multiple gestations requires careful clinical assessment. This may be achieved through pelvic ultrasonography, monitoring of estrogen levels, and/or clinical evaluation of estrogen activity.

Generally, an initial dose of 75 IU/day, administered by subcutaneous route, for 5 to 7 days is recommended. If there is no apparent ovarian response, the daily dose is gradually increased until estrogen levels start to rise. A daily ascent rate of 40 to 100% is considered to be optimal. The daily effective dose is maintained until preovulatory conditions are reached. If estrogen levels rise too rapidly (i.e., more than a daily doubling for 2 consecutive days), the daily dose should be decreased. Preovulatory conditions are reached when plasma estradiol levels of 1000 to 3000 pmol/L are attained, and/or when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in mean diameter. Usually, 7 to 14 days of treatment is sufficient to reach this state. Once preovulatory conditions are reached, the administration of *FostiRel™* should be discontinued and ovulation induced by administration of 5000 to 10000 IU human chorionic-gonadotropin (hCG).

Beginning the day prior to administration of human chorionic gonadotropin the couple should be encouraged to have intercourse at least 3 times per week until ovulation occurs.

Clinical confirmation of ovulation is obtained through the indices of progesterone production. Increasing progesterone secretion by the corpus luteum and a concomitant increase in basal body temperature are indirect signs of ovulation. A serum progesterone level over 30 nmol/L also provides adequate proof of a functional corpus luteum. Lower concentrations of serum progesterone may be supplemented by luteal phase injections of hCG. Within the following 9 days after the initial hCG administration, 2 to 3 injections of 1000 to 3000 IU hCG each may be given to prevent insufficiency of the corpus luteum.

Patients should be closely monitored for 2 weeks following *FostiRel™* and hCG treatment to ensure that hyperstimulation does not occur. If the ovaries become abnormally enlarged, there is more than a 1 kg/day gain in weight, or abdominal pain occurs, administration of hCG should be stopped. Most ovarian hyperstimulation occurs after follitropin beta treatment has been completed and reaches its maximum at about 7 to 10 days after hCG administration (see Warnings).

#### Dosage in males

*FostiRel™* should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

There is no relevant indication for use of *FostiRel™* in children.

### ADMINISTRATION

The best site for subcutaneous administration of *FostiRel™* injection is in the abdomen around the navel. Pinch up a large area of skin between the finger and thumb. Vary the injection site with each injection. The needle should be inserted at the base of the pinched-up skin at a 45° angle. Subcutaneous injection of *FostiRel™* may be carried out by patients or their partners, provided proper instructions are given by the physician. Self-administration of *FostiRel™* should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

### General information

If you miss or forget a dose, do not double your next dose. Contact your health-care provider for recommendations.

Do not mix *FostiRel™* with any other medicines in the same vial or in the same syringe.

### STORAGE

#### Storage by pharmacist

Store at 2°C – 8°C (in a refrigerator). Do not freeze.

#### Storage by patients

Store at 2°C – 8°C (in a refrigerator). Do not freeze.

### SHELF LIFE

The vial should be used for a maximum of 21 days from the first withdrawal. Drug should be withdrawn using insulin syringe. Discard unused contents of the vial after 21 days from the first withdrawal. Shelf life of *FostiRel™* multi-dose vials and pre-filled syringes is 24 months from the date of manufacturing.

### PRESENTATION

*FostiRel™* Multi dose vial of 0.4 ml / 1.2 ml / 1.6 ml/ 2.7ml containing 750 IU per ml.

*FostiRel™* Pre-filled syringe of 0.1/0.2/0.3 ml containing 750 IU per ml.

*FostiRel™* is a sterile clear colorless liquid in a multi-dose vial along with pack insert in a carton or as a single-dose pre-filled syringe.

  
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