דצמבר 2022

Gonal-f, Solution for Injection גונאל-אף
Follitropin Alfa 600 IU/mL

רופא/ה, רוקח/ת וצוות רפואי נכבדים,

אנו מבקשים להודיעכם כי העלון לרופא והוראות השימוש (IFU) של התכשיר **Gonal-f** עודכנו.

<u>ההתוויות המאושרות:</u>

<u>In adult women:</u>

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.
- Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT).
- Follitropin alfa in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.

<u>In adult men:</u>

- Follitropin alfa is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.

השינויים בעלון לרופא הינם:

4. CLINICAL PARTICULARS
4.4 Special warnings and precautions for use
(…)
Ovarian Hyperstimulation Syndrome (OHSS)
A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degree of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

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The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events such as pulmonary embolism, ischemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum ~~o~~estradiol levels ~~(e.g. > 900 pg/mL or > 3,300 pmol/L in anovulation; > 3,000 pg/mL or > 11,000 pmol/L in ART)~~ and previous episodes of OHSS, large number of developing ovarian follicles ~~(e.g. > 3 follicles of ≥ 14 mm in diameter in anovulation; ≥ 20 follicles of ≥ 12 mm in diameter in ART)~~ and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended GONAL-f dose, regimen of administration can minimise the risk of ovarian hyperstimulation (see sections 4.2 and 4.8). Monitoring of stimulation cycles by ultrasound scans as well as estradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur such as serum estradiol level > 5,500 pg/mL or > 20,200 pmol/L and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days. OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Therefore patients should be followed for at least two weeks after hCG administration.

In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped if still ongoing, and that the patient be hospitalised and appropriate therapy be started.
(…)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(…)

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

~~In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the object of~~

~~GONAL-f therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.~~

Pharmacodynamic effects
Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.
(…)

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

Distribution
Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of 14 to 17 hours ~~about one day~~. The steady state volume of distribution is in the range of 9 to 11 L ~~and total clearance are 10 l and 0.6 l/h, respectively. One-eighth of the follitropin alfa dose is excreted in the urine~~.

Following subcutaneous administration, the absolute bioavailability is ~~about 70~~ 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to~~–~~ 4 days. ~~In women whose endogenous gonadotropin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.~~

Elimination
Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine.

בנוסף לכתוב מעלה, עודכנו הוראות השימוש בתכשיר, העדכונים כוללים שינויי נוסח בלבד.

למידע המלא יש בעלון לרופא, לצרכן ובהוראות השימוש כפי שאושרו על ידי משרד הבריאות.

העלונים לרופא, לצרכן והוראות השימוש מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום מרק סרונו בע"מ, רח' הקישון 18, יבנה 81220, טל' 09-9510737

בברכה,

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