SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bemfola 300 IU/0.50 mL solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the solution contains 600 IU (equivalent to 44 micrograms) of follitropin alfa*. Each pre-filled pen delivers 300 IU (equivalent to 22 micrograms) in 0.5 mL.

* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear colourless solution.

The pH of the solution is 6.7 to 7.3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.

- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer.
- Follitropin alfa in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

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

4.2 Posology and method of administration

Treatment with follitropin alfa should be initiated under the supervision of a physician experienced in the treatment of fertility disorders.

Patients must be provided with the correct number of pens for their treatment course and educated to use the proper injection techniques.

Posology

Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should be individualised to optimise follicular development and to minimise the risk of unwanted ovarian hyperstimulation. It is advised to adhere to the recommended starting doses indicated below.

Women with anovulation (including polycystic ovarian syndrome)
Follitropin alfa may be given as a course of daily injections. In menstruating women treatment should commence within the first 7 days of the menstrual cycle.

In the registration trials, a commonly used regimen commenced at 75 to 150 IU FSH daily and was increased preferably by 37.5 or 75 IU at 7 or preferably 14-day intervals if necessary, to obtain an adequate, but not excessive, response.

In clinical practice, the starting dose is typically individualised based on the patient's clinical characteristics, such as markers of ovarian reserve, age, body mass index, and, if applicable, previous ovarian response to ovarian stimulation.

Starting dose
The starting dose can be adjusted in a stepwise manner (a) lower than 75 IU per day if an excessive ovarian response in terms of number of follicles is anticipated based on the patient's clinical profile (age, body mass index, ovarian reserve); or (b) higher than 75 up to a maximum of 150 IU per day may be considered if a low ovarian response is anticipated.
The patient's response should be closely monitored by measuring follicle size and number by ultrasound and/or estrogen secretion.

Dose adjustments
If a patient fails to respond adequately (either low or excessive ovarian response), continuation of that treatment cycle should be evaluated and managed according to the physician's standard of care. In cases of low response, the daily dose should not exceed 225 IU FSH.

If an excessive ovarian response is obtained according to the physician's assessment, treatment should be stopped and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a dose lower than that of the previous cycle.

Final follicular maturation
When an optimal ovarian response is obtained, a single injection of 250 micrograms recombinant human choriogonadotropin alfa (r-hCG) or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last follitropin alfa injection. The patient is recommended to have coitus on the day of, and the day following hCG administration. Alternatively, intrauterine insemination may be performed.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
In the registration trials a commonly used regimen for superovulation involved the administration of 150 to 225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. In clinical practice, the starting dose is typically individualised based on the patient's clinical characteristics, such as markers of ovarian reserve, age, body mass index, and, if applicable, previous ovarian response to ovarian stimulation.

Starting dose
If a low ovarian response is anticipated, the starting dose may be adjusted in a stepwise manner to not higher than 450 IU daily. Conversely, if an excessive ovarian response is expected, the starting dose may be decreased below 150 IU.
The patient's response should continue to be closely monitored by measuring follicle size and number by ultrasound and/or estrogen secretion until adequate follicular development has been achieved. Bemfola can be given either alone, or, to prevent premature luteinisation, in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist.

Dose adjustments
If a patient fails to respond adequately (either low or excessive ovarian response), continuation of that treatment cycle should be evaluated and managed according to the physician's standard of care. In cases of low response, the daily dose should not exceed 450 IU FSH.

Final follicular maturation
When an optimal ovarian response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 48 hours after the last follitropin alfa injection to induce final follicular maturation.

Women with severe LH and FSH deficiency
In LH and FSH deficient women, the objective of follitropin alfa therapy in

association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75 to 150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and estrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7 to 14-day intervals and preferably by 37.5 to 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last follitropin alfa and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following hCG administration.Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician’s judgment of the clinical case.

Luteal phase support may be considered since lack of substances with luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum.

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

Men with hypogonadotrophic hypogonadism
Follitropin alfa should be given at a dose of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

Special populations

Elderly
There is no relevant use of follitropin alfa in the elderly population. Safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
Safety, efficacy and pharmacokinetics of follitropin alfa in patients with renal or hepatic impairment have not been established.

Paediatric population
There is no relevant use of follitropin alfa in the paediatric population.

Method of administration

Bemfola is intended for subcutaneous use. The injection should be given at the same time each day.

The first injection of Bemfola should be performed under direct medical supervision. Self-administration of Bemfola should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

The injection site should be alternated daily.

As the Bemfola pre-filled pen with the single-dose cartridge is intended for only one injection, clear instructions should be provided to the patients to avoid misuse of the single dose presentation.

For instructions on the administration with the pre-filled pen, see section 6.6 and the package leaflet.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- tumours of the hypothalamus or pituitary gland;
- ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin;
- gynaecological haemorrhages of unknown origin;
- ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as in cases of:
- primary ovarian failure;
- malformations of sexual organs incompatible with pregnancy;
- fibroid tumours of the uterus incompatible with pregnancy;
- primary testicular insufficiency.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Follitropin alfa is a potent gonadotrophic substance capable of causing mild to severe adverse reactions and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotropin therapy requires a certain time commitment by physicians and supportive health care professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of follitropin alfa calls for

monitoring of the ovarian response with ultrasound, alone or preferably in combination with measurement of serum estradiol levels, on a regular basis. There may be a degree of inter-patient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with follitropin alfa. Deterioration or a first appearance of this condition may require cessation of treatment.

Treatment in women

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether as treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to the recommended follitropin alfa dose and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. For accurate interpretation of the indices of follicle development and maturation, the physician should be experienced in the interpretation of the relevant tests.

In clinical trials, an increase of the ovarian sensitivity to follitropin alfa was shown when administered with lutropin alfa. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7 to 14-day intervals and preferably with 37.5 to 75 IU increments.

No direct comparison of follitropin alfa/LH versus human menopausal gonadotropin (hMG) has been performed. Comparison with historical data suggests that the ovulation rate obtained with follitropin alfa/LH is similar to that obtained with hMG.

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 degrees 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.

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, ischaemic 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 estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended follitropin alfa dose and 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, 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.

Multiple pregnancy
In patients undergoing ovulation induction, the incidence of a multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancy, especially of high order, carries an increased risk of adverse maternal and perinatal outcomes.

To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.

The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy loss
The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception.

Ectopic pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART was reported to be higher than in the general population.

Reproductive system neoplasms
There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

Congenital malformation
The prevalence 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 pregnancies.

Thromboembolic events
In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

Treatment in men

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to follitropin alfa/hCG therapy. Follitropin alfa should not be used when an effective response cannot be obtained.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of follitropin alfa with other medicinal products used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dose of follitropin alfa needed to elicit an adequate ovarian response. No other clinically significant medicinal product interaction has been reported during follitropin alfa therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no indication for use of follitropin alfa during pregnancy. Data on a limited number of exposed pregnancies (less than 300 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of follitropin alfa.

No teratogenic effect has been observed in animal studies (see section 5.3). In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa.

Breastfeeding

Follitropin alfa is not indicated during breastfeeding.

Fertility

Follitropin alfa is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

Follitropin alfa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection).

Mild or moderate ovarian hyperstimulation syndrome (OHSS) has been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Treatment in women

Immune system disorders
Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Nervous system disorders
Very common: Headache

Vascular disorders
Very rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders
Very rare: Exacerbation or aggravation of asthma

Gastrointestinal disorders
Common: Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea

Reproductive system and breast disorders
Very common: Ovarian cysts
Common: Mild or moderate OHSS (including associated symptomatology)
Uncommon: Severe OHSS (including associated symptomatology) (see section 4.4)
Rare: Complication of severe OHSS

General disorders and administration site conditions
Very common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Treatment in men

Immune system disorders
Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Respiratory, thoracic and mediastinal disorders
Very rare: Exacerbation or aggravation of asthma

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders
Common: Gynaecomastia, varicocele

General disorders and administration site conditions
Very common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Investigations
Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The effects of an overdose of follitropin alfa are unknown, nevertheless, there is a possibility that OHSS may occur (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins, ATC code: G03GA05.

Bemfola is a biosimilar medicinal product.

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.

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.

Clinical efficacy and safety in women

In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level < 1.2 IU/L as measured in a central laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In clinical studies comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table below) and in ovulation induction, follitropin alfa was more potent than urinary FSH in terms of a lower total dose and a shorter treatment period needed to trigger follicular maturation.

In ART, follitropin alfa at a lower total dose and shorter treatment period than urinary FSH, resulted in a higher number of oocytes retrieved when compared to urinary FSH.

Table: Results of study GF 8407 (randomised parallel group study comparing efficacy and safety of follitropin alfa with urinary FSH in assisted reproduction technologies)

	follitropin alfa (n = 130)	urinary FSH (n = 116)
Number of oocytes retrieved	11.0 ± 5.9	8.8 ± 4.8
Days of FSH stimulation required	11.7 ± 1.9	14.5 ± 3.3
Total dose of FSH required (number of FSH 75 IU ampoules)	27.6 ± 10.2	40.7 ± 13.6
Need to increase the dose (%)	56.2	85.3

Differences between the 2 groups were statistically significant ($p < 0.05$) for all criteria listed.

Clinical efficacy and safety in men

In men deficient in FSH, follitropin alfa administered concomitantly with hCG for at least 4 months induces spermatogenesis.

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. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 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.

Elimination

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity and genotoxicity in addition to those already stated in the other sections of this SmPC.

Impaired fertility has been reported in rats exposed to pharmacological doses of follitropin alfa (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

Given in high doses (≥ 5 IU/kg/day) follitropin alfa caused a decrease in the number of viable foetuses without being teratogenic, and dystocia similar to that observed with urinary menopausal gonadotropin (hMG). However, since follitropin alfa is not indicated in pregnancy, these data are of limited clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poloxamer 188
Sucrose
Methionine
Disodium phosphate dihydrate

Sodium dihydrogen phosphate dihydrate
Phosphoric acid
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Once opened, the medicinal product should be injected immediately.

6.4 Special precautions for storage

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

Before opening and within its shelf life, the medicinal product may be removed from the refrigerator, and without being refrigerated again, may be stored for up to 3 months at or below 25°C. The medicinal product must be discarded if it has not been used after 3 months.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

1.5 mL cartridge (type I glass), with a plunger stopper (halobutyl rubber) and an aluminium crimp cap with a rubber inlay, assembled in a pre-filled pen.

Each cartridge contains 0.5 mL solution for injection.

Pack sizes of 1, 5 and 10 pre-filled pens including one disposable needle and alcohol swab per pen. One needle and one alcohol swab to be used with the pen for administration.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution should not be administered if it contains particles or is not clear.

Bemfola pre-filled pen is not designed to allow the cartridge to be removed.

Discard used pen and needle immediately after injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For instructions on the administration with the pre-filled pen, see the package leaflet.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04854/0169

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

30/06/2025