ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 75 IU/0.125 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 75 IU (equivalent to 5.5 micrograms) in 0.125 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 - 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian syndrome, PCOS) 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 (GIFT) and zygote intra-fallopian 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.

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 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

The dose recommendations given for follitropin alfa are those in use for urinary FSH. Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical trials have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

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.

A commonly used regimen commences at 75-150 IU FSH daily and is 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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotropin alfa (r-hCG) or 5,000 IU up to 10,000 IU hCG should be administered 24-48 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 (IUI) may be performed.

If an excessive response is obtained, 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.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
A commonly used regimen for superovulation involves the administration of 150-225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Women with anovulation resulting from severe LH and FSH deficiency
In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the

oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 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 7-14 day intervals and preferably by 37.5-75 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 24-48 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, IUI may be performed.

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.

Men with hypogonadotropic 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 population
There is no relevant use of follitropin alfa in the elderly population. The safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
The 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 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.

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 not due to polycystic ovarian syndrome;
- gynaecological haemorrhages of unknown aetiology;
- 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.

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 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 reason for the couple's infertility must be thoroughly investigated and putative contraindications for pregnancy must be evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and should be treated accordingly.

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 7-14 day intervals and preferably with 37.5-75 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 polycystic ovarian syndrome, high absolute or rapidly rising serum 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 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).

Adherence to the recommended follitropin alfa dose and to the 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 a 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.

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 a multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures the risk of a 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, regardless of 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 pregnant women (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.

Breast-feeding

Follitropin alfa is not indicated during breast-feeding.

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 is expected to have 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 adverse reactions are ranked under heading of frequency using the following convention: 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 the national reporting system listed in Appendix V.

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. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of therapy with follitropin alfa is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

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 trials comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 1 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 1: 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

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and is eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution 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%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady state within 3-4 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.

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 ($\geq$ 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 0.125 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 and other handling

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

Bemfola 75 IU/0.125 mL (5.5 micrograms/0.125 mL) 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)

EU/1/13/909/001
EU/1/13/909/006
EU/1/13/909/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/03/2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 150 IU/0.25 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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* 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.

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- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian 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.

In adult men

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4.2 Posology and method of administration

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

Posology

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Comparative clinical trials have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

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.

A commonly used regimen commences at 75-150 IU FSH daily and is 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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotropin alfa (r-hCG) or 5,000 IU up to 10,000 IU hCG should be administered 24-48 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 (IUI) may be performed.

If an excessive response is obtained, 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.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
A commonly used regimen for superovulation involves the administration of 150-225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Women with anovulation resulting from severe LH and FSH deficiency
In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the

oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 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 7-14 day intervals and preferably by 37.5-75 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 24-48 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, IUI may be performed.

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.

Men with hypogonadotropic 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 population
There is no relevant use of follitropin alfa in the elderly population. The safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
The 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 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.

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 not due to polycystic ovarian syndrome;
- gynaecological haemorrhages of unknown aetiology;
- ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as in case 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.

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 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 reason for the couple's infertility must be thoroughly investigated and putative contraindications for pregnancy must be evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and should be treated accordingly.

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 7-14 day intervals and preferably with 37.5-75 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 polycystic ovarian syndrome, high absolute or rapidly rising serum oestradiol 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 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).

Adherence to the recommended follitropin alfa dose and to the 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 a 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.

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 a 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, regardless of 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 pregnant women (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.

Breast-feeding

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 is expected to have 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 adverse reactions are ranked under heading of frequency using the following convention: 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 the national reporting system listed in Appendix V.

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. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of therapy with follitropin alfa is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

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 trials comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 1 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 1: 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

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and is eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution 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%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steadystate within 3-4 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.

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 ($\geq$ 40 IU/kg/day) for extended periods, through reduced fecundity.

Given in high doses ($\geq$ 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 0.25 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 and other handling

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

Bemfola 150 IU/0.25 mL (11 micrograms/0.25 mL) 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)

EU/1/13/909/002
EU/1/13/909/008
EU/1/13/909/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/03/2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 225 IU/0.375 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 225 IU (equivalent to 16.5 micrograms) in 0.375 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 - 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovariansyndrome, PCOS) 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 (GIFT) and zygote intra-fallopian 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.

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 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

The dose recommendations given for follitropin alfa are those in use for urinary FSH. Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical trials have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

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.

A commonly used regimen commences at 75-150 IU FSH daily and is 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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotropin alfa (r-hCG) or 5,000 IU up to 10,000 IU hCG should be administered 24-48 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 (IUI) may be performed.

If an excessive response is obtained, 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.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
A commonly used regimen for superovulation involves the administration of 150-225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Women with anovulation resulting from severe LH and FSH deficiency
In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the

oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 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 7-14 day intervals and preferably by 37.5-75 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 24-48 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, IUI may be performed.

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.

Men with hypogonadotropic 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 population
There is no relevant use of follitropin alfa in the elderly population. The safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
The 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 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.

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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 not due to polycystic ovarian syndrome;
- gynaecological haemorrhages of unknown aetiology;
- ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as in case 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.

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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 reason for the couple's infertility must be thoroughly investigated and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and should be treated accordingly.

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 7-14 day intervals and preferably with 37.5-75 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 polycystic ovarian syndrome high absolute or rapidly rising serum oestradiol 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 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).

Adherence to the recommended follitropin alfa dose and to the 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 oestradiol 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 a 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.

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 a 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, regardless of 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 pregnant women (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 is expected to have 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 adverse reactions are ranked under heading of frequency using the following convention: 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 the national reporting system listed in Appendix V.

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. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of therapy with follitropin alfa is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

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 trials comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 1 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 1: 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

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and is eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution 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%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady state within 3-4 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.

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 ($\geq$ 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 0.375 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 and other handling

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

Bemfola 225 IU/0.375 mL (16.5 micrograms/0.375 mL) 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)

EU/1/13/909/003
EU/1/13/909/010
EU/1/13/909/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/03/2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

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 - 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian syndrome, PCOs) 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 (GIFT) and zygote intra-fallopian 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.

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 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

The dose recommendations given for follitropin alfa are those in use for urinary FSH. Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical trials have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

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.

A commonly used regimen commences at 75-150 IU FSH daily and is 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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotropin alfa (r-hCG) or 5,000 IU up to 10,000 IU hCG should be administered 24-48 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 (IUI) may be performed.

If an excessive response is obtained, 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.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
A commonly used regimen for superovulation involves the administration of 150-225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Women with anovulation resulting from severe LH and FSH deficiency
In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the

oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 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 7-14 day intervals and preferably by 37.5-75 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 24-48 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, IUI may be performed.

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.

Men with hypogonadotropic 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 population
There is no relevant use of follitropin alfa in the elderly population. The safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
The 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 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.

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 not due to polycystic ovarian syndrome;
- gynaecological haemorrhages of unknown aetiology;
- ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as in case 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.

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 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 interpatient 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 reason for the couple's infertility must be assessed thoroughly investigated and putative contraindications for pregnancy must be evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and should be treated accordingly.

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 7-14 day intervals and preferably with 37.5-75 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 polycystic ovarian syndrome high absolute or rapidly rising serum oestradiol 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 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).

Adherence to the recommended follitropin alfa dose and to the 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 oestradiol 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 a 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.

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 a 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, regardless of 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 pregnant women (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.

Breast-feeding
Follitropin alfa is not indicated during breast-feeding.

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 is expected to have 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 adverse reactions are ranked under heading of frequency using the following convention: 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 the national reporting system listed in Appendix V.

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. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of therapy with follitropin alfa is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

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 trials comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 1 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 1: 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

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and is eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution 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%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steadystate within 3-4 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.

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 other sections of this SmPC.

Impaired fertility has been reported in rats exposed to pharmacological doses of follitropin alfa ($\geq$ 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 and other handling

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

Bemfola 300 IU/0.50 mL (22 micrograms/0.5 mL) 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)

EU/1/13/909/004
EU/1/13/909/012
EU/1/13/909/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/03/2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 450 IU/0.75 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 450 IU (equivalent to 33 micrograms) in 0.75 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 - 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian snydrome, PCOS) 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 (GIFT) and zygote intra-fallopian 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.

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 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

The dose recommendations given for follitropin alfa are those in use for urinary FSH. Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical trials have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

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.

A commonly used regimen commences at 75-150 IU FSH daily and is 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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotropin alfa (r-hCG) or 5,000 IU up to 10,000 IU hCG should be administered 24-48 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 (IUI) may be performed.

If an excessive response is obtained, 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.

Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies
A commonly used regimen for superovulation involves the administration of 150-225 IU of follitropin alfa daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Women with anovulation resulting from severe LH and FSH deficiency
In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the

oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous estrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 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 7-14 day intervals and preferably by 37.5-75 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 24-48 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, IUI may be performed.

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.

Men with hypogonadotropic 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 population
There is no relevant use of follitropin alfa in the elderly population. The safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment
The 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 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.

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 not due to polycystic ovarian syndrome;
- gynaecological haemorrhages of unknown aetiology;
- ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as in case 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.

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 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 interpatient 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 reason for the couple's infertility must be thoroughly investigated and putative contraindications for pregnancy must be evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and should be treated accordingly.

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 clinicaltrials, 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 7-14 day intervals and preferably with 37.5-75 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 polycystic ovarian syndrome, high absolute or rapidly rising serum oestradiol 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 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).

Adherence to the recommended follitropin alfa dose and to the 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 oestradiol 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 oestradiol 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.

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 a 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, regardless of 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 pregnant women (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 is expected to have 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, usually associated with severe OHSS (see section 4.4).

List of adverse reactions

The adverse reactions are ranked under heading of frequency using the following convention: 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 the national reporting system listed in Appendix V.

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. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of therapy with follitropin alfa is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

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 trials comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 1 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 1: 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

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and is eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution 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%. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steadystate within 3-4 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.

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 ($\geq$ 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 0.75 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 and other handling

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

Bemfola 450 IU/0.75 mL (33 micrograms/0.75 mL) 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)

EU/1/13/909/005
EU/1/13/909/014
EU/1/13/909/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/03/2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Polymun Scientific Immunbiologische Forschung GmbH
Donaustraße 99
Klosterneuburg 3400
Austria

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1, 5 OR 10 PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 75 IU/0.125 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen delivers 75 IU follitropin alfa, equivalent to 5.5 micrograms per 0.125 mL. Each mL of the solution contains 600 IU equivalent to 44 micrograms.

3. LIST OF EXCIPIENTS

Poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 injection needle
1 alcohol swab

5 pre-filled pens
5 injection needles
5 alcohol swabs

10 pre-filled pens
10 injection needles
10 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

Within its shelf-life, the unopened product may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/909/001
EU/1/13/909/006
EU/1/13/909/007

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bemfola 75 IU/0.125 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bemfola 75 IU/0.125 mL injection
follitropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.125 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 5 OR 10 PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 150 IU/0.25 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen delivers 150 IU follitropin alfa, equivalent to 11 micrograms per 0.25 mL. Each mL of the solution contains 600 IU equivalent to 44 micrograms.

3. LIST OF EXCIPIENTS

Poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 injection needle
1 alcohol swab

5 pre-filled pens
5 injection needles
5 alcohol swabs

10 pre-filled pens
10 injection needles
10 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

Within its shelf-life, the unopened product may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/909/002
EU/1/13/909/008
EU/1/13/909/009

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bemfola 150 IU/0.25 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bemfola 150 IU/0.25 mL injection
follitropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.25 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 5 OR 10 PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 225 IU/0.375 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen delivers 225 IU follitropin alfa, equivalent to 16.5 micrograms per 0.375 mL. Each mL of the solution contains 600 IU equivalent to 44 micrograms.

3. LIST OF EXCIPIENTS

Poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 injection needle
1 alcohol swab

5 pre-filled pens
5 injection needles
5 alcohol swabs

10 pre-filled pens
10 injection needles
10 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

Within its shelf-life, the unopened product may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/909/003
EU/1/13/909/010
EU/1/13/909/011

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bemfola 225 IU/0.375 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bemfola 225 IU/0.375 mL injection
follitropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.375 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 5 OR 10 PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 300 IU/0.5 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen delivers 300 IU follitropin alfa, equivalent to 22 micrograms per 0.5 mL. Each mL of the solution contains 600 IU equivalent to 44 micrograms.

3. LIST OF EXCIPIENTS

Poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 injection needle
1 alcohol swab

5 pre-filled pens
5 injection needles
5 alcohol swabs

10 pre-filled pens
10 injection needles
10 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

Within its shelf-life, the unopened product may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/909/004
EU/1/13/909/012
EU/1/13/909/013

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bemfola 300 IU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bemfola 300 IU/0.5 mL injection
follitropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 5 OR 10 PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Bemfola 450 IU/0.75 mL solution for injection in pre-filled pen
follitropin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen delivers 450 IU follitropin alfa, equivalent to 33 micrograms per 0.75 mL. Each mL of the solution contains 600 IU equivalent to 44 micrograms.

3. LIST OF EXCIPIENTS

Poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 injection needle
1 alcohol swab

5 pre-filled pens
5 injection needles
5 alcohol swabs

10 pre-filled pens
10 injection needles
10 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

Within its shelf-life, the unopened product may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/909/005
EU/1/13/909/014
EU/1/13/909/015

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bemfola 450 IU/0.75 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bemfola 450 IU/0.75 mL injection
follitropin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.75 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bemfola 75 IU/0.125 mL solution for injection in pre-filled pen
Bemfola 150 IU/0.25 mL solution for injection in pre-filled pen
Bemfola 225 IU/0.375 mL solution for injection in pre-filled pen
Bemfola 300 IU/0.50 mL solution for injection in pre-filled pen
Bemfola 450 IU/0.75 mL solution for injection in pre-filled pen

follitropin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects,talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bemfola is and what it is used for

What Bemfola is
This medicine contains the active substance follitropin alfa, which is almost identical to a natural hormone produced by your body called “follicle-stimulating hormone” (FSH). FSH is a gonadotropin, a type of hormone that plays an important role in human fertility and reproduction. In women, FSH is needed for the growth and development of the sacs (follicles) in the ovaries that contain the egg cells. In men, FSH is needed for the production of sperm.

What Bemfola is used for

In adult women, Bemfola is used:
- to help release an egg from the ovary (ovulation) in women that cannot ovulate and that did not respond to treatment with a medicine called “clomiphene citrate”.
- together with another medicine called “lutropin alfa” (“luteinising hormone” or LH) to help release an egg from the ovary (ovulation) in women that are not ovulating because their body is producing very little gonadotropins (FSH and LH).
- to help develop several follicles (each containing an egg) in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “in vitro fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.

In adult men, Bemfola is used:
- together with another medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to a low level of certain hormones.

2. What you need to know before you use Bemfola

You and your partner's fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Do not use Bemfola
- if you are allergic to follicle stimulating hormone or any of the other ingredients of this medicine (listed in section 6).
- if you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).
- If you are **a woman**:
  - with large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
  - with unexplained vaginal bleeding.
  - with cancer in your ovaries, womb or breasts.
  - with a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.
- If you are **a man**:
  - with damaged testicles that cannot be healed.

Do not use Bemfola if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

Warnings and precautions
Porphyria
Tell your doctor before you start treatment, if you or any member of your family have porphyria (an inability to break down porphyrins that may be passed on from parents to children).
Tell your doctor straight away if:
- your skin becomes fragile and easily blistered, especially skin that has been frequently in the sun, and/or
- you have stomach, arm or leg pain.

In case of the above events your doctor may recommend that you stop treatment.

Ovarian Hyper-Stimulation Syndrome (OHSS)
If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts. If you get lower abdominal pain, gain any weight rapidly, feel sick or are vomiting or if you have difficulty in breathing, talk to your doctor straight away who might ask you to stop using this medicine (see section 4).
In case you are not ovulating, and if the recommended dose and schedule of administration are adhered to, the occurrence of OHSS is less likely. Bemfola treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, hCG) is administered. If you are developing OHSS your doctor may not give you any hCG in this treatment cycle and you may be told not to have sex or to use a barrier contraceptive method for at least four days.

Multiple pregnancy
When using Bemfola, you have a higher risk of being pregnant with more than one child at the same time ("multiple pregnancy", mostly twins), than if you conceive naturally. A multiple pregnancy may lead to medical complications for you and your babies. You can reduce the risk of multiple pregnancy by using the right dose of Bemfola at the right times. When undergoing assisted reproductive technology the risk of having a multiple pregnancy is related to your age, the quality and the number of fertilised eggs or embryos placed inside you**.**

Miscarriage
When undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs, you are more likely to have a miscarriage than the average woman.

Blood clotting problems (thromboembolic events)

If you had in the past or recently blood clots in the leg or in the lung, or a heart attack or stroke, or if those happened in your family, then you might have a higher risk that these problems occur or become worse with Bemfola treatment.

Men with too much FSH in their blood
If you are a man, having too much FSH in your blood can be a sign of damaged testicles. Bemfola usually does not work if you have this problem. If your doctor decides to try Bemfola treatment, to monitor the treatment, they may ask you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents
Bemfola is not indicated for use in children and adolescents under 18 years of age.

Other medicines and Bemfola
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
- If you use Bemfola with other medicines which help ovulation (such as hCG or clomiphene citrate), this may increase the response of your follicles.
- If you use Bemfola at the same time as a "gonadotropin-releasing hormone" (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of Bemfola to produce follicles.

Pregnancy and breast-feeding
Do not use Bemfola if you are pregnant or breast-feeding.

Driving and using machines
It is not expected that this medicine will affect your ability to drive and use machines.

Bemfola contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to use Bemfola

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine

- Bemfola is intended to be given by injection just under the skin (subcutaneously). Use the pre-filled pen only once then it should be disposed of in a safe manner. Do not administered the solution if it contains particles or is not clear.
- The first injection of Bemfola should be given under supervision of your doctor.
- Your doctor or nurse will show you how to use the Bemfola pre-filled pen to inject the medicine.
- If you administer Bemfola to yourself, please carefully read and follow the "Instructions for Use". These instructions can be found at the end of the package leaflet.

How much to use

Your doctor will decide how much medicine you will use and how often. The doses described below are stated in International Units (IU) and millilitres (mL).

Women

If you are not ovulating and have irregular or no periods

- Bemfola is usually given every day.
- If you have irregular periods, start using Bemfola within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of Bemfola is 75 to 150 IU (0.12 to 0.25 mL) each day.
- Your dose of Bemfola may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response or your doctor tells you to stop, see below.
- The maximum daily dose of Bemfola is usually not higher than 225 IU (0.375 mL).
- When you get the desired response, you will be given a single injection of 250 micrograms of "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5,000 to 10,000 IU of hCG, 24 to 48 hours after your last Bemfola injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with Bemfola should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of Bemfola than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, OHSS). For the following cycle, your doctor will give you a lower dose of Bemfola than before.

If you are not ovulating, have no periods and have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of Bemfola is 75 to 150 IU (0.12 to 0.25 mL) together with 75 IU (0.12 mL) of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of Bemfola may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5,000 to 10,000 IU of hCG, 24 to 48 hours after your last injections of Bemfola and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination may be performed by placing the sperm into the womb cavity.

If your doctor cannot see a response after 5 weeks, that treatment cycle with Bemfola should be stopped. For the following cycle, your doctor will give you a higher starting dose of Bemfola than before.

If your body responds too strongly, your treatment with Bemfola will be stopped and you will not be given any hCG (see section 2, OHSS). For the following cycle, your doctor will give you a lower dose of Bemfola than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of Bemfola is 150 to 225 IU (0.25 to 0.37 mL) each day, from day 2 or 3 of your treatment cycle.
- Bemfola dose may be increased, depending on your response. The maximum daily dose is 450 IU (0.75 mL).
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or

5,000 IU to 10,000 IU of hCG, 24 to 48 hours after the last Bemfola injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then Bemfola is started approximately two weeks after start of agonist treatment. The Bemfola and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU Bemfola is administered for 7 days. The dose is then adjusted according to your ovarian response. When GnRH antagonist is used, it is administered from the 5th or 6th day of Bemfola treatment and continued until ovulation induction.

Men

- The usual dose of Bemfola is 150 IU (0.25 mL) together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more Bemfola than you should

The effects of taking too much Bemfola are unknown. Nevertheless one could expect Ovarian Hyper-Stimulation Syndrome (OHSS) to occur, which is described in section 4. However the OHSS will only occur if hCG is also administered (see section 2, under 'OHSS').

If you forget to use Bemfola

If you forget to use Bemfola, do not take a double dose to make up for a forgotten dose. Please talk to your doctor as soon as you notice that you forgot a dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects in women

- Lower abdominal pain together with nausea or vomiting may be the symptoms of Ovarian Hyper-Stimulation Syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed (see also section 2 "Take special care with Bemfola"). This side effect is common (may affect up to 1 in 10 people).
- OHSS may become severe with clearly enlarged ovaries, decreased urine production, weight gain, difficulty in breathing and/or possible fluid accumulation in your stomach or chest. This side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1,000 people).
- Serious blood clotting complications (thromboembolic events) sometimes independent of OHSS may be found very rarely (may affect up to 1 in 10,000 people). This could cause chest pain, breathlessness, stroke or heart attack (see also section 2 under 'Blood clotting problems').

Serious side effects in men and women

- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing can sometimes be serious. This side effect is very rare

If you notice any of the above-listed side effects you should immediately contact your doctor, who might ask you to stop using Bemfola.

Other side effects in women

Very common (may affect more than 1 in 10 people):
- Sacs of fluid within the ovaries (ovarian cysts)
- Headache
- Local reactions at the injection site, such as pain, redness, bruising, swelling and/or irritation

Common (may affect up to 1 in 10 people):
- Abdominal pain
- Feeling sick, vomiting, diarrhoea, abdominal cramps and bloating

Very rare (may affect up to 1 in 10,000 people):
- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse

Other side effects in men

Very common (may affect more than 1 in 10 people):
- Local reactions at the injection site, such as pain, redness, bruising, swelling and/or irritation

Common (may affect up to 1 in 10 people):
- Swelling of the veins above and behind the testicles (varicocele).
- Breast development, acne or weight gain.

Very rare (may affect up to 1 in 10,000 people):
- Allergic reactions such as rash, red skin, hives, swelling of your face with difficulty in breathing may occur. These reactions can sometimes be serious.
- Your asthma may get worse.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bemfola

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the pen label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.

Within its shelf life, the unopened pen may be stored at or below 25°C for up to 3 months without being refrigerated again and must be discarded if it has not been used after 3 months.

Do not use this medicine if you notice any visible signs of deterioration, if the liquid contains particles or is not clear.

Once opened, the medicine should be injected immediately.

Do not throw any medicines away via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Bemfola contains

- The active substance is follitropin alfa.

- Bemfola 75 IU/0.125 mL: Each cartridge contains 75 IU (equivalent to 5.5 micrograms) follitropin alfa in 0.125 mL solution.
- Bemfola 150 IU/0.25 mL: Each cartridge contains 150 IU (equivalent to 11 micrograms) follitropin alfa in 0.25 mL solution.
- Bemfola 225 IU/0.375 mL: Each cartridge contains 225 IU (equivalent to 16.5 micrograms) follitropin alfa in 0.375 mL solution.
- Bemfola 300 IU/0.50 mL: Each cartridge contains 300 IU (equivalent to 22 micrograms) follitropin alfa in 0.50 mL solution.
- Bemfola 450 IU/0.75 mL: Each cartridge contains 450 IU (equivalent to 33 micrograms) follitropin alfa in 0.75 mL solution.
- Each mL of the solution contains 600 IU (equivalent to 44 micrograms) follitropin alfa.
- The other ingredients are poloxamer 188, sucrose, methionine, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid and water for injections.

What Bemfola looks like and contents of the pack

- Bemfola is presented as a clear, colourless liquid for injection in a pre-filled pen (injection).
- Bemfola is supplied in packs with 1, 5 or 10 pre-filled pens, 1, 5 or 10 disposable needles and 1, 5 or 10 alcohol swabs. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Bemfola 75 IU/0.125 mL pre-filled pen
Bemfola 150 IU/0.25 mL pre-filled pen
Bemfola 225 IU/0.375 mL pre-filled pen
Bemfola 300 IU/0.50 mL pre-filled pen
Bemfola 450 IU/0.75 mL pre-filled pen

Instructions for use

CONTENTS

1. How to use the Bemfola pre-filled pen

- Before starting to use your pre-filled pen, please read these instructions and the package leaflet the whole way through first.
- Only use this pen for you – do not let anyone else use it.
- The numbers on the dose display are measured in International Units or IU. **Your doctor will have told you how many IU to inject each day.**
- **Your doctor/pharmacist will tell you how many Bemfola pens you need to use for your complete treatment course.**
- Give yourself the injection around the same time each day.

2. Before you start using your pre-filled pen

2.1. Wash your hands

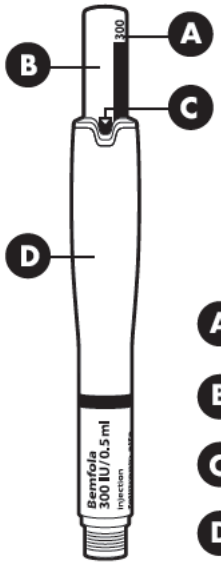
- It is important that your hands and the things you use to get your pen ready are as clean as possible.

2.2. Find a clean area

- A good place is a clean table or surface.

3. Getting your pre-filled pen ready for injection

The different parts of your pen

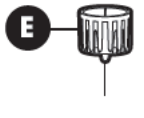


A Dosage

B Dosage knob

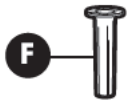
C Activation bar

D Cartridge with medication

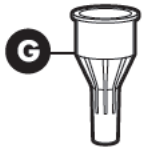


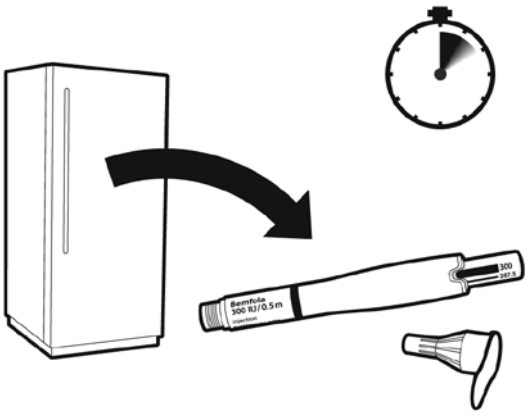
E Needle

F Inner needle cap

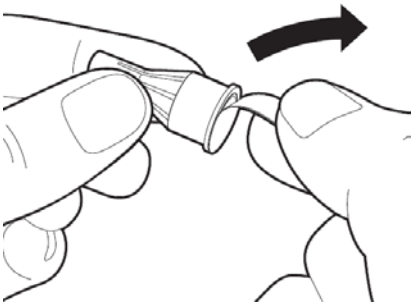


G Outer needle cap

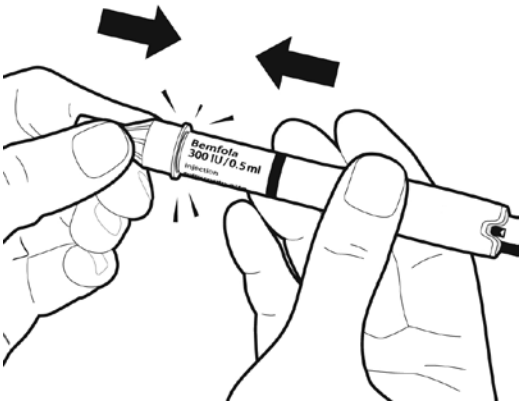




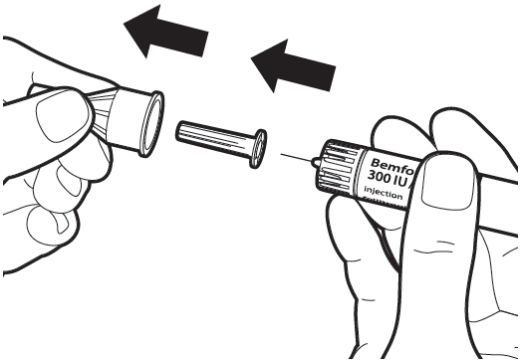
Perform the injection every day around the same time. Take the pen out of the fridge 5 to 10 minutes before using it. Note: Please check that the medicine is not frozen.



Remove the peel tab from the injection needle.



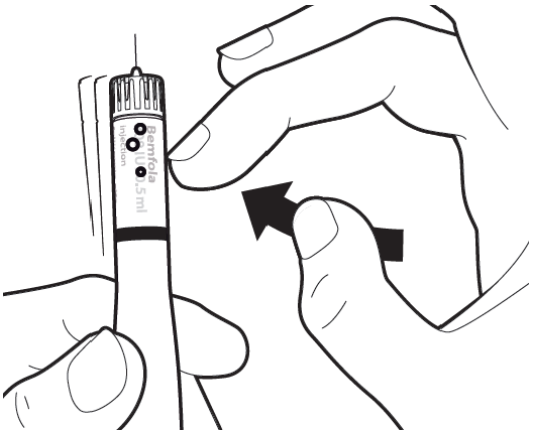
Hold the pen by its sides and attach the needle by clicking it into place. Do not twist it on. You will hear a click when it is securely fixed.
Caution:
Do not push the dosage knob in while attaching the needle.



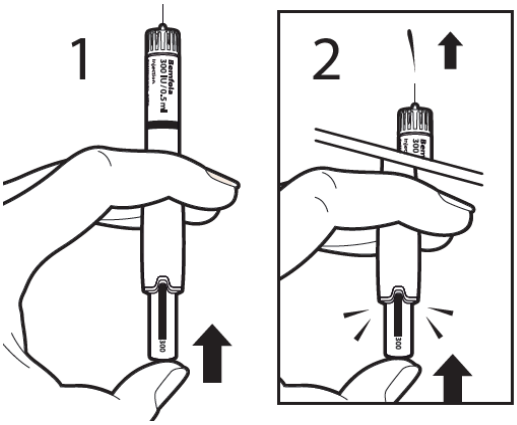
Remove the outer needle cap. **Keep it for later. You will need it after the injection.**

Remove the inner needle cap.

4. Setting the dose

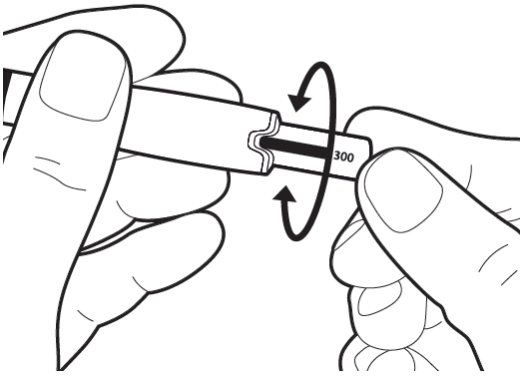


Hold the pen so that the needle is pointing upright. Gently tap the pen so that any large
air bubbles rise to the top.



Still holding the pen
upright, push the dosage knob in
until the activation
bar with the small arrow disappears. You should also hear a click, and some liquid will splash out (this is normal).The pen is now ready to set the dose.

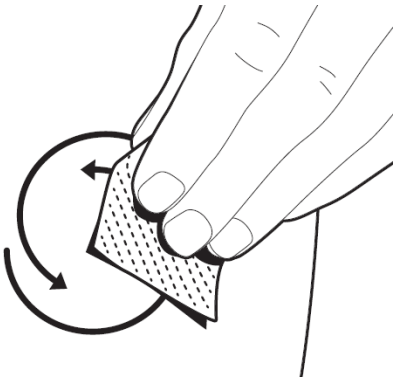
If no liquid splashes out, the pen should not be used.



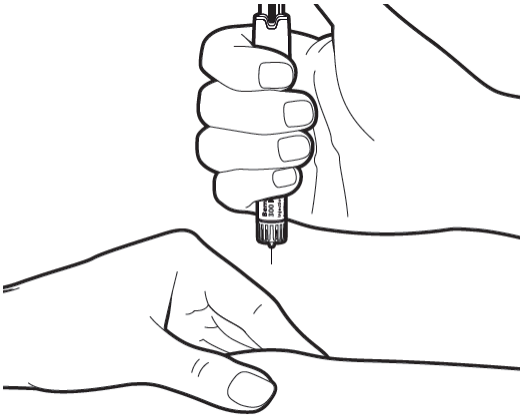
Turn the dosage knob until your prescribed dose is in line with the display window.
Note: The pen is now ready for injection.
Caution:
Do not push the dosage knob in any further, at this point.

5. Injecting the dose

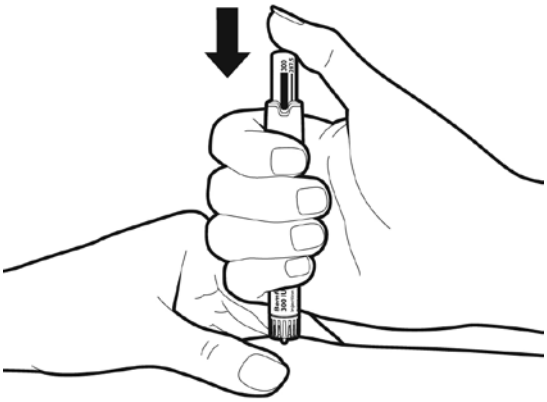
Now you are ready to immediately give yourself the injection: Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). To minimise skin irritation, select a different injection site each day.



Clean the injection site with the alcohol swab using a circular motion.

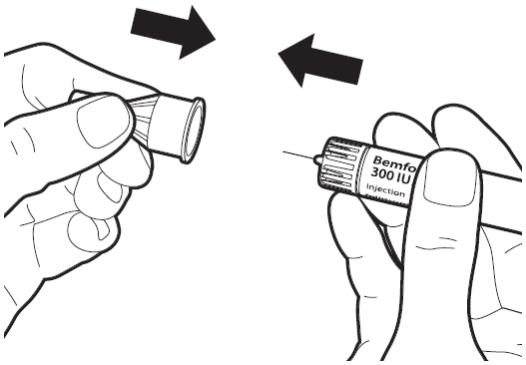


Lightly pinch the skin of the injection area. Hold the pen at approximately a right angle and insert the needle completely in a steady movement.
Caution: Do not push the dosage knob, while inserting the needle.

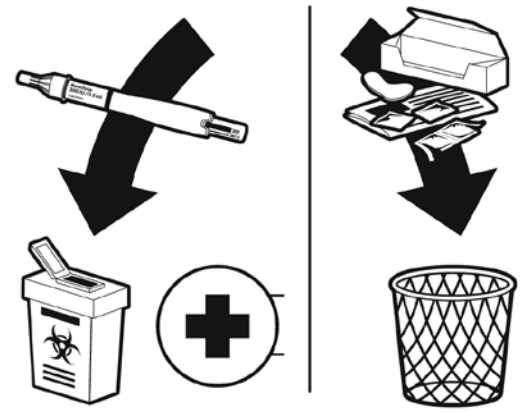


Push in the dosage knob slowly and continuously until it stops, and the dose bar has disappeared.
Do not remove the needle immediately, wait for **5 seconds**, before pulling it out.
After the withdrawal of the needle: clean the skin with an alcohol swab using a circular motion.

6. After the injection



Replace the outer needle cap onto the needle carefully.



Throw away the packaging box, inner needle cap, peel tab, alcohol swab and the instructions for use in the normal household waste. Do not throw away any medicines via your sink, toilet or in your household waste. The used pen needs to be discarded in a sharps container and returned to the pharmacy for a correct disposal. Ask your pharmacist how to dispose of medicines you no longer use.