GEDEON RICHTER

Bemfola® Frequently Asked Questions

VERSION NO. 4 REPLACING ALL PREVIOUS VERSIONS OF BEMFOLA® FAQ DOCUMENTS

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Pharmaceutical properties, including storage and stability

1. How do I store Bemfola®?

Bemfola® should be store in a refrigerator (2°C - 8°C). Do not freeze.
Before opening, Bemfola® may be removed from the refrigerator, without being refrigerated again, for up to 3 months at or below 25°C. The product must be discarded if it has not been used after 3 months.
Store in the original package in order to protect from light.

Reference:
SmPC Section 6.4

2. After Bemfola® is removed from the refrigerator, how long can it be stored at room temperature?

Once Bemfola® is removed from the refrigerator, it can be stored for up to 3 months at 25°C or below.
If the product was not used after these 3 months, it should be discarded.

Reference:
SmPC Section 6.4

3. What is the shelf-life of Bemfola®?

The shelf-life of the product is 3 years if stored in a refrigerator at 2°C to 8°C.
Reference:
SmPC, section 6.3

4. Can you use the product after the expiry date?

No, the product must be discarded once it has reached the end of its shelf-life.
Reference:
SmPC, sections 6.3 and 6.4

5. Can I leave the pen exposed to light?

No, the product must be stored in the original packaging.
Exposure to light during the pen preparation and administration is not a concern, but ensure that the pen is stored prior to use in the original packaging.

Reference:
SMPC Section 6.4
Tests have been conducted on impact of light on FSH, demonstrating that there are no major effects, and as a precautionary measure the product should be stored in original packaging until use.

6. Can I use the pen at a high altitude or carry it on a plane?

Yes, but it is important that the pen is not exposed to extremes of temperature more than 25°C and lower than 2°C.

Reference:
SMPC Section 6.4

7. How should Bemfola® be transported?

After receiving the product, take the product home immediately, do not leave the product exposed to elevated temperatures (max 25°C), especially in summer, or let it fall below 2°C, especially in winter.
If the transport time is long (>1 hour), place the product into a 'cool-bag' to avoid any substantial changes of temperature.

Reference:
SMPC Section 6.4

8. Will the pen break if it is dropped?

An accidental fall during transportation or administration should not damage the pen. However, always check to see if any component has been damaged, or if there is any sign of product leakage and ensure the position of the arrow is visible. If all of these are OK, then the product can be used.

9. How do I dispose of the used product and accessories?

Used Bemfola® pens should be discarded safely according to the instructions provided by the clinic e.g. into 'Sharps container' and returned to the pharmacy, clinic or hospital for safe disposal.

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

The packaging box, white inner needle cap, peel tab and the instructions for use can be thrown in your normal household waste.

Local disposal / recycling regulations should be followed.

Reference:
SMPC Section 6.6

10. Can I use Bemfola® if it was stored outside the refrigerator?

Yes, Bemfola® can be stored up to 25°C for a maximum of three months.

Reference:
SmPC, section 6.3

11. Is Bemfola® filled by mass?

Yes, Bemfola® is filled by mass.
For example, in the 75 presentation each prefilled pen delivers 75 IU, which is equivalent to 5.5 micrograms in 0.125 ml.

Reference:
SmPC, section 2

12. What are the differences between Bemfola® and GONAL-f® in terms of cell line and manufacturing process?

The follitropin alfa in Bemfola®, as well as in the reference product GONAL-f®, is produced by recombinant DNA technology. Both products are made in Chinese hamster ovary cell (CHO) line. The genes to make human FSH are introduced into the CHO cell, which then produces the FSH molecule.

References:
SmPC Bemfola®, section 2
SmPC GONAL-f®, section 2

13. How is the stability and standardization ensured?

Bemfola® is manufactured according to the same standards as other biotech medicines, and regulatory authorities perform periodic inspection to our manufacturing site.
The stability of Bemfola® is repeatedly tested in long-term stability studies. These studies are defined by internationally recognized health authority's guidelines.
On a regular basis, batches are tested for stability under different conditions for up to 3 years, to monitor the validity of the shelf life as approved by the health authorities.
To ensure stability, Bemfola® is stored and transported as a 'cold chain' product. A cold chain is a temperature-controlled supply chain. Bemfola® is transported in an unbroken cold chain, which is an uninterrupted series of refrigerated production, storage and distribution activities, along with associated equipment and logistics, which maintain a desired low-temperature range.
Additionally, Bemfola® can be stored up to 3 months at room temperature.

References:
SmPC, section 6.4
Marketing Authorization (EMA)

Composition/formulation

14. What is the active ingredient in Bemfola®?

Bemfola® contains recombinant human follicle stimulating hormone (r-hFSH) (termed follitropin-alfa), which is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Reference:
SmPC, section 2

15. What are the dose adjustments for the Bemfola® pens?

All pens are pre-filled and allows for reduced dose adjustments in 12.5 IU increments.

16. What are the presentations of the Bemfola® pens?

Bemfola® is available as 75 IU, 150 IU, 225 IU, 300 IU, 450 pre-filled pens.

Reference:
Bemfola® Package Leaflet

17. What are the r-hFSH concentrations in the Bemfola® pens?

Each ml of the solution contains 600 IU (equivalent to 44 micrograms) of follitropin alfa

- Each prefilled pen delivers 75 IU (equivalent to 5.5 micrograms) in 0.125 ml.
- Each prefilled pen delivers 150 IU (equivalent to 11 micrograms) in 0.25 ml.
- Each prefilled pen delivers 225 IU (equivalent to 16.5 micrograms) in 0.375 ml.
- Each prefilled pen delivers 300 IU (equivalent to 22 micrograms) in 0.5 ml.
- Each prefilled pen delivers 450 IU (equivalent to 33 micrograms) in 0.75 ml.

Reference:
SmPC, sections 2

18. What excipients does Bemfola® contain?

- Poloxamer 188
- Sucrose
- Methionine
- Disodium hydrogen phosphate dihydrate
- Sodium dihydrogen phosphate dihydrate
- Phosphoric acid
- Water for injections

Reference:
SmPC section 6.1

19. Do the components of the product contains preservatives?

No, Bemfola® doesn't contain any preservatives. Having no preservative allows Bemfola tom have a 3-year shelf life instead of 2 years for GONAL-f® in prefilled pens.

Reference:
SmPC, section 6.1 and 6.3

20. Is Bemfola® latex and gluten free?

Yes, Bemfola® is latex and gluten free.

Reference:
Data on file

21. Are you using fetal calf serum in the production of Bemfola®?

No, active product ingredient in Bemfola® is produced in a CHO cell line. The entire manufacturing process, from the first cloning of the master cell bank to the filled Bemfola® pens, is completely serum-free.

References:
Data on file

22. How is the batch-to-batch consistency of Bemfola® ensured?

Human FSH is a complex glycoprotein (sugar molecules attached to a protein backbone) which in nature is subject to a degree of variability. As the active substance, follitropin alfa in Bemfola® is also made in living cells, there can be some variability in the sugar molecules attached to the protein backbone. This inherent degree of minor variability is also called “microheterogeneity”. The degree of this variability must fall within an acceptable range to ensure consistent safety and

efficacy. This is done by adjusting our manufacturing processes to guarantee that the active substance fits into the desired specifications range.

Bemfola® batch release tests, consistently fall within the range of batch-to-batch variation of the reference medicine to ensure that it does not affect the way the product work or its safety. Every batch must meet specifications prior to being released for use in the market. It has been noted that some of the observed variations (for Bemfola) are smaller than those allowed for follitropin in the European Pharmacopoeia monograph"

References:

- European Medicines Agency: Similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf
- European Medicines Agency: Similar biological medicinal products (overarching guideline). CHMP/437/07 Rev.1 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
- Bemfola EPAR

Posology dosing/administration

23. Why do I need to prime the pen?

The mechanical action of the delivery system must be activated after the needle insertion to ensure that the selected dose can be completely delivered.

Reference:
Data on file
Bemfola package leaflet

24. What is the overfill in Bemfola® pens?

The overfill in the pens is a small amount of extra medication that ensures the drug content shown on the product label can be administered fully.

Reference:
Data on file

25. Can the overfill be used as part of a dose?

No, only the selected dose or the nominal maximum dose per pen can be injected.

Reference:
SmPC section 1

26. How should Bemfola® be administered?

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.

Using this medicine:
• Bemfola® is intended to be given by injection just under the skin (subcutaneously). The prefilled pen is to be used only once and then thrown away. The solution should not be administered if it contains particles or is not clear.
• The first injection of Bemfola® should be given under supervision of a physician.
• A physician or a nurse should show the patient how to use the Bemfola pre-filled pen to inject the medicine.
• If the patient is to administer Bemfola® to herself, she should read carefully and follow the “Instructions for use”. These instructions can be found at the end of the package leaflet.

Reference:
Package leaflet

27. What are the dosing recommendations for Bemfola®?

For women with anovulation (including polycystic ovarian syndrome)

Bemfola® 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 Bemfola® 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. 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 Bemfola 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

Bemfola 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.

Reference:

SmPC, section 4.2

Bemfola® Package Leaflet

28. What to do in case of excessive ovarian response during treatment?

If an excessive ovarian response is obtained, treatment should be stopped and hCG (to induce final follicular maturation) withheld. 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.

Reference:
SmPC, section 4.2

29. Can Bemfola® be used in renal/hepatic impaired patients?

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

Reference:
SmPC, section 4.2

30. What to do if a dose of Bemfola® was missed?

Patients should be informed not to take a double dose to make up for the forgotten one and inform their treating physician immediately.

Reference:
Bemfola® Package Leaflet

31. Do the Bemfola® pens allow adjustment for the dose to be administered?

Yes, each Bemfola® pen allows the dose to be altered within the ranges below in increments of 12.5IU:
75 IU Bemfola®pen - delivers a dose from 37.5 IU to 75 IU
150 IU Bemfola®pen - delivers a dose from 75 IU to 150 IU
225 IU Bemfola®pen - delivers a dose from 150 IU to 225 IU
300 IU Bemfola®pen - delivers a dose from 225 IU to 300 IU
450 IU Bemfola®pen - delivers a dose from 300 IU to 450 IU
To provide the following possible doses:

75 UI 0,125 ml	**150 UI** 0,25 ml	**225 UI** 0,375 ml	**300 UI** 0,50 ml	**450 UI** 0,75 ml
37,5 UI 50 UI 62,5 UI **75 UI**	75 UI 87,5 UI 100 UI 112,5 UI 125 UI 137,5 UI **150 UI**	150 UI 162,5 UI 175 UI 187,5 UI 200 UI 212,5 UI **225 UI**	225 UI 237,5 UI 250 UI 262,5 UI 275 UI 287,5 UI **300 UI**	300 UI 325 UI 337,5 UI 350 UI 375 UI 400 UI 421,5 UI 425 UI **450 UI**

Reference:
SmPC section 1

Efficacy

32. What are the approved therapeutic indications for Bemfola®?

The following therapeutic indications are approved with for Bemfola®:

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:

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.

Reference:
SmPC, section 4.1

33. What is the serum half- life of Bemfola®?

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day.

Reference:
SmPC, section 5.2

34. What is the bioavailability of Bemfola®?

Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, Bemfola® accumulates 3-fold achieving a steady state within 3-4 days.

Reference:
SmPC, section 5.2

35. What are the clinical effects of Bemfola®?

Follicle-stimulating hormone, as it name indicates, stimulates follicular growth and maturation. Therefore, FSH is used in controlled ovarian stimulation.
The goal of ovarian stimulation is to induce ongoing development of multiple large follicles and to have mature oocytes. Thus, ovarian stimulation enables the retrieval of multiple oocytes resulting in having several embryos to choose from for transfer. This will improve chances for conception.

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.

The physician identifies the presumably most appropriate regimen, in terms of gonadotropin-releasing hormone (GnRH) analog protocol, FSH formulation, starting FSH dose, and combination of different gonadotropins, following the evaluation of demographic, anthropometric, and ovarian reserve profiles.

References:

- SmPC, section 5.1
- Endocr Rev. 2006 Apr;27(2):170-207. Epub 2006 Jan 24.
  The science behind 25 years of ovarian stimulation for in vitro fertilization. Macklon NS, Stouffer RL, Giudice LC, Fauser BC.

Safety

36. What are the potential side effects of Bemfola®?

The most common side effects with Bemfola (which may affect more than 1 in 10 people) are reactions at the injection site (pain, redness, bruising, swelling or irritation). In women, ovarian cysts (sacs of fluid within the ovaries) and headache are also seen in more than 1 patient in 10. For the full list of all side effects reported with Bemfola, please see the full SmPC.

Some women, can over-respond to stimulation and mild or moderate ovarian hyperstimulation syndrome (OHSS) has been commonly reported and should be considered as an intrinsic risk of the ovarian stimulation procedure. Severe OHSS is uncommon. Thromboembolism may occur very rarely, usually associated with severe OHSS.

Reference:
SmPC section 4.8

37. Can Bemfola® be used during pregnancy or lactation?

There is no indication for use of Bemfola 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. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa. However, in case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa. Bemfola® is not indicated during breastfeeding.

Reference:
SmPC section 4.6 and 5.3

38. Does the usage of Bemfola® have any effects on the ability to drive and use machines?

Bemfola® is expected to have no or negligible influence on the ability to drive and use machines.

Reference:
SmPC, section 4.7

39. What are the effects in the case of a potential overdose of Bemfola®?

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

Reference:
SmPC, section 4.4 and 4.9

40. Is there an increased risk of immunogenicity with Bemfola®?

Immunogenicity is always studied for biological medicines. This is because of the intrinsic ability of proteins and other biological medicines to cause an unwanted immune response, which, in rare cases, could cause a serious adverse reaction (e.g. anaphylaxis or delayed hypersensitivity) or reduced efficacy.

Experience shows that, a harmful immune response is unlikely after a change to the manufacturing process of a biological medicine, since comparability studies prove that the batch from the new process is of the same quality and free of impurities or aggregates that can trigger immunogenicity.

Biological medicines usually cause no or only a limited immune response (e.g. transient appearance of antibodies). Adverse reactions of an immune nature (e.g. infusion-related reactions or injection-site reactions) are normally not severe. Rarely, however, an immune reaction against a biological medicine could be serious and life-threatening. Also, antibodies directed against the biological medicine ('anti-drug antibodies' or ADAs) could neutralise the medicine's activity and reduce its efficacy. Thus, potential immunogenicity needs to be always evaluated for all biological medicines. Glycosylation patterns, the major determinants of immunogenicity, are very similar between Bemfola® and GONAL-f®. Immunogenicity was directly measured in a phase 3 clinical study. None of the patients in the study showed any evidence of anti-FSH antibodies, even after repeated treatment cycles. There is also no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines.

References:

- Rettenbacher M, et al. Reproductive BioMedicine Online (2015) 30, 504–513
- Biosimilars in the EU. Informatino guide for healthcare professionals. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (last access 14 Sep 2017)
- European Medicines Agency: Immunogenicity assessment of biotechnology-derived therapeutic proteins. EMEA/CHMP/BMWP/14327/2006.
- http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf
- Kurki P, van Aerts L, Wolff-Holz E, et al. Interchangeability of biosimilars: A European perspective. BioDrugs 2017,31:83-91
- Weise M, Kurki P, Wolff-Holz, et al. Biosimilars: the science of extrapolation. Blood 2014;124(22):3191-6

41. How does your company ensure the pharmacovigilance of Bemfola®?

Apart from reactions of an immunological nature, must adverse drug reactions (ADRs) can be predicted from the pharmacological action, and occur with both the reference medicine and Bemfola®.
Of more than 25 biosimilars approved in the EU to date, none have been withdrawn or suspended for safety or efficacy reasons.
All medicines, Bemfola® included, are subject to pharmacovigilance requirements, including a detailed risk management plan (RMP) and pharmacovigilance master file.
Prescribers and patients using any type of medicines are encouraged to report any unusual side effects to enable any differences to the reference medicine to be detected.

Gedeon Richter, in compliance with the Pharmacovigilance regulations, collects all reports of suspected ADRs (Adverse drug reactions) and submits periodic safety update reports (PSURs) to regulators.

Reference:
http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

42. How to report suspected adverse reactions of Bemfola®?

To report an adverse event, safety event, quality complaint or request for medical information:
Please insert your contact details
Phone number: your local phone number

- Adverse Event E-mail: DrugSafety@richter.hu (if you have a local email, please provide it)
- Medical Information: 'medinfo@richter.hu' (if you have a local email, please provide it)
- Complaints : 'Quality complaints' <Qualitycomplaints@richter.hu>

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 their national reporting system. Patients should immediately contact their treating doctor or pharmacist when suspecting a potential side effect after using Bemfola®.

References:

- SmPC, section 4.8
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac05800241de

43. What does the black triangle in the Bemfola® box, SMPC and package leaflet mean?

The black triangle symbol means that; "This medicinal product is subject to ongoing additional monitoring".
Ongoing monitoring encourages healthcare professionals and patients to report any suspected adverse drug reactions of new medicines. This enables prompt identification and analysis of information about the medicines to add to the knowledge gained during clinical trials. **These triangle symbol, does not necessarily mean that there are additional safety concerns with it.**
All new medicines are closely monitored after being introduced to the market. Biological medicines approved after 1 January 2011 are subject to so called 'additional monitoring' and are included in a list of medicines under 'additional monitoring'.

Reference:
http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

Contra-indication /warnings /interactions

44. Who should not use Bemfola®?

Bemfola® must not be used in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in SmPC 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.

Reference:
SmPC, section 4.3 and 6.1

45. What are the warnings and precautions to use Bemfola®?

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.

Ovarian stimulation with Bemfola® should always be monitored with ultrasound, preferably in combination with measurement of serum oestradiol levels, on a regular basis. 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 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 dosage 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. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

Multiple pregnancy

In patients undergoing ovulation induction, the incidence of multiple pregnancy is increased compared with natural conception. Multiple pregnancy, especially of high

order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risk of multiple births before starting treatment.

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
Bemfola® contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially "sodium-free".

Reference:
SmPC, section 4.4

46. Are there interactions of Bemfola® with other medicinal products?

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.

Reference:
SmPC, section 4.5

47. Can Bemfola® be used during pregnancy?

No, there is no indication for use of Bemfola 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. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa.

Reference:
SmPC, section 4.6

48. Can Bemfola® be used during breast-feeding?

No, Bemfola® is not indicated during breastfeeding.

Reference:
SmPC, section 4.6

Other considerations

49. What are the available pharmaceutical forms and contents?

Solution for injection in a pre-filled pen.
Doses of:

- 75 IU/0.125 ml (5.5 micrograms)
- 150 IU/0.25 ml (11 micrograms)
- 225 IU/0.375 ml (16.5 micrograms)
- 300 IU/0.50 ml (22 micrograms)
- 450 IU/0.75 ml (33 micrograms)

Solution for injection in boxes of 1, 5 or 10 pre-filled pens:

Reference:
SmPC section 1

50. Does the use of Bemfola® pens cause more wastage than the other available gonadotrophins?

No, Bemfola® is provided as a daily disposable pen which enables, in most treatment cycles, the exact dose to be provided potentially reducing drug wastage.

In the minority of IVF cycles non-standard dosages are used; and in standard dosages there is less wastage with Bemfola®.
One of the main differences between FSH products is their delivery devices. Bemfola® is provided in a 75, 150, 225, 300 or 450 IU adjustable daily dose pen d. In contrast, GONAL-f® is provided as 75 IU vials or multi-dose pen devices (300, 450, and 900 IU), while Menopur® is provided as 75 IU vials and 600 or 1200 IU multi-dose vials.

With the multidose products (GONAL-f® / Puregon®), where 900 cartridges are used, often the patients are given three 900 pens (2700 IU) and then they only use 225 IU or 2500 IU and throw away the remainder.
If the dose changes during the cycle, then with multidose products the patient will either have to inject twice to avoid wastage or will waste whatever product is left in the cartridge.

When estimating treatment costs, studies often only include the drug acquisition costs. However, wastage associated cost might also have an impact on overall treatment costs as not every IU of drug is used during a treatment

Reference:
Foxon et al. Hum Fertil (Camb). 2017 May 26:1-6

51. How can the presentations of Bemfola® help to minimize wastage?

When estimating treatment costs, studies often only include the drug acquisition costs. However, wastage associated cost might also have an impact on overall treatment costs. as not every IU of drug is used during a treatment.

Bemfola® is provided as a daily disposable device which enables, in most treatment cycles, the exact dose to be provided potentially reducing drug wastage. Most analysed treatment cycles had an FSH starting dose corresponding to the maximum dose contained within one daily dose pen device (150, 225, 300 IU). Use of daily pen devices would result in no wastage under the condition that FSH doses are not adjusted after the gonadotropin stimulation has commenced.

Reference:

Foxon et al. Hum Fertil (Camb). 2017 May 26:1-6

52. What is the difference between biosimilars and generics?

A generic is a chemically synthesized medicine usually a simple (such as aspirin), homogeneous small molecule, whose bioequivalence to a reference medicine can be easily demonstrated. However, a biosimilar is a medicine of biological origin with a complex protein structure, usually heterogeneous, and requiring extensive molecular characterization. Because of that heterogeneity, any variation from the reference medicine must be assessed to ensure that there is no therapeutic consequence for the patient. Biosimilarity, is demonstrated through clinical comparisons of efficacy and safety. Therefore, the regulatory requirements for the development of biosimilars are more demanding than for generics.

Table 1: Fundamental differences

Chemical drugs	Biologic drugs
Made by chemical synthesis	Made by living cells
Defined structure	Heterogeneous structure Mixtures of related molecules
Easy to characterise	Difficult to characterise
Relatively stable	Variable Sensitive to environmental conditions
Usually taken orally	Usually injected
Often prescribed by a general practitioner	Usually prescribed by specialists Immuogenicity

Source: Duke University School of Medicine

Reference:

http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

53. What material do you use to manufacture the pen? Is it recyclable and eco-friendly?

The 0.125 ml of solution for injection in a 1.5 ml cartridge is made of a type I glass, with a plunger stopper (halobutyl rubber) and an aluminum crimp cap with a rubber inlay. The plastic and resin from the colors are formulated to comply with the European food contact regulation EC Directive 2002/72/EC. All plastics fulfill the bio-comparability requirements according to ISO 10993 and thus are environmentally acceptable.

Reference:
SMPC Bemfola®

54. Who is the manufacturer of the biological active substance of Bemfola®?

Polymun Scientific Immunbiologische Forschung
GmbH Donaustraße 99
Klosterneuburg 3400
Austria

Reference:
SmPC, Annex II

55. Who is responsible for the batch release of Bemfola®?

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

Reference:
SmPC, Annex II

56. What is the Red Dot award?

The red dot design award is an international design award. The committee grants this award in distinct categories. We won this award for our DuoPen injection system, which is the injection system used for Bemfola®.

Reference:
http://en.red-dot.org/2037.html