EMA/83300/2014

Summary of the risk management plan (RMP) for Bemfola (follitropin alfa)

This is a summary of the risk management plan (RMP) for Bemfola, which details the measures to be taken in order to ensure that Bemfola is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Bemfola, which can be found on Bemfola's EPAR page.

Overview of disease epidemiology

Bemfola is a biosimilar medicine (similar to a biological medicine also known as the 'reference medicine' that is already authorised in the EU). The reference medicine for Bemfola is Gonal-f. Both are licensed in the management of certain forms of infertility:

- Anovulation (failure to produce eggs, including because of a condition called polycystic ovary disease or PCOD) in women who have been unresponsive to treatment with another medicine called clomiphene citrate.

  The proportion of women with anovulation unresponsive to clomiphene citrate is unknown. The overall frequency of chronic (long-term) anovulation in women during their reproductive years has been estimated to be 6 to 15%. In 90% of affected individuals, anovulation is due to PCOD (a complex syndrome associated with reduced fertility, hormone disturbances, and the presence of fluid-filled cysts in the ovaries).

- Stimulation of multifollicular development (development of more than one egg-releasing follicle at a time in the ovary) in patients undergoing superovulation (multiple egg production) for assisted reproductive technologies (ART).

- Stimulation (in association with a luteinising hormone, or LH, preparation) of follicular development in women with severe deficiency (very low levels) of LH and follicle-stimulating hormone (FSH).

  LH deficiency is uncommon on its own and almost always occurs together with FSH deficiency because they are both produced by the same cells in the pituitary gland (a part of the brain). Stress-related reduction in these hormones, leading to reduced function of the reproductive system (hypogonadotrophic hypogonadism) accounts for more than 30% of cases of loss of menstruation (secondary amenorrhoea) in women of reproductive age.

  Failure of the pituitary gland to work properly occurs in approximately 33% of women with secondary amenorrhea, of whom about one-third have a tumour of the pituitary gland.

- Stimulation of spermatogenesis (sperm production) in men who have congenital (inborn) or acquired hypogonadotrophic hypogonadism. Bemfola is used with another hormone, human chorionic gonadotrophin (hCG).

  Male infertility is probably responsible for one-third of the 10% to 15% of couples who are unable to conceive within one year of unprotected intercourse. Most of these male-associated cases result

from diminished, absent, or faulty sperm production. FSH plays an important role in spermatogenesis.

Summary of treatment benefits

Because Bemfola is a biosimilar medicine, studies were designed to compare Bemfola with its reference medicine Gonal-f, which also contains follitropin alfa as active substance. Studies in people have been limited to tests to determine that Bemfola behaves similarly to Gonal-f both in terms of its blood levels over time and of its ability to stimulate the ovaries to produce more than one egg:

- Study FIN1001 is a small study performed in 24 healthy female volunteers aged 18-28 years and aimed to compare over time the blood levels of Bemfola with those of Gonal-f after a single injection under the skin.
- Study FIN3001 is a large controlled study which aimed to compare whether Bemfola and Gonal-f are similar in terms of their efficacy (how well the medicine works) and safety (side effects). The study was performed in 372 women aged between 20 and 38 years undergoing ART.

The blood levels over time obtained for Bemfola and Gonal-f observed in study FIN1001 demonstrated similarity between both follitropin alfa-containing medicinal products.

The main measure of effectiveness in study FIN3001 was the average number of eggs (oocytes) retrieved per patient. The average number of oocytes retrieved was 10.7 in the Bemfola group (246 subjects) and 10.4 in the Gonal-f group (123 subjects). This study showed that Bemfola was as effective as Gonal-f at stimulating the ovaries during assisted reproductive techniques. Other measures of effectiveness (including dose of follitropin alfa, number of days of stimulation and number of patients with cycle cancellation) were comparable between the Bemfola and Gonal-f groups.

Unknowns relating to treatment benefits

Because the studies with Bemfola were designed to establish its similarity to Gonal-f, any uncertainties regarding its benefits are considered to be the same as for the reference medicine.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Ovarian hyperstimulation syndrome (OHSS, when the ovaries over-respond to treatment)	OHSS is a known risk for follitropin alfa. Symptoms can range from mild abdominal discomfort to severe conditions requiring hospitalisation. In study FIN3001 a higher incidence of OHSS during the first treatment cycle was observed for Bemfola when compared with Gonal-f (22.1% vs. 13.0% of treated patients). In the second treatment cycle there were no imbalances between the Bemfola and Gonal-f groups. The difference in the first treatment cycle could be	The Summary of Product Characteristics (SmPC) for Bemfola, which contains information for doctors, includes a warning on the risk of OHSS in section 4.4 and lists this side effect in section 4.8.

Risk	What is known	Preventability
	due to chance. Further studies are ongoing to clarify the issue.	
Hypersensitivity (allergic) reactions (including anaphylactic reactions).	Mild and severe hypersensitivity reactions have been observed with Bemfola's reference product, Gonal-f.	Avoid use of Bemfola in subjects hypersensitive to follitropin alfa, FSH or to any of the excipients of Bemfola. See SmPC section 4.3 (contraindications).
Thromboembolic events (blood clots), usually with OHSS.	Thromboembolic events have been observed during severe cases of OHSS.	Several warnings have been introduced in the SmPC: Warning in section 4.4 stating that *"Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction".* Furthermore, a separate paragraph in section 4.4 entitled "Thromboembolic events" describes risk factors for thromboembolic events. Included in section 4.8 under vascular disorders, *"Very rare: Thromboembolism, usually associated with severe OHSS (see Section 4.4)."*
Worsening of asthma	Worsening of asthma has been observed for Bemfola's reference product Gonal-f, so it is likely that similar reactions will occur with Bemfola.	Bemfola is a prescription-only medicine. Introduced in section 4.8 of the SmPC: "*Very rare: Exacerbation or aggravation of asthma*."
Multiple pregnancies (twins, etc.)	Multiple pregnancies have been observed for Bemfola and the reference product Gonal-f. It is known that induction of superovulation and assisted reproductive technology treatment are per se associated with an increased risk of multiple pregnancies.	Warning introduced in section 4.4 of the SmPC alerting prescribers of the increased risk of multiple pregnancies and that multiple pregnancies carry an increased risk of adverse maternal and perinatal outcomes. The warning advises prescribers to carefully monitor ovarian response and advises patients of the potential risks of multiple births before starting treatment.
Gynaecomastia (enlarged	Gynaecomastia has been	Listed in section 4.8 as a

Risk	What is known	Preventability
breasts in males)	observed for the reference product Gonal-f, so it is likely that similar reactions will also occur with Bemfola when used in men.	common adverse event. "Common: Gynaecomastia." Prescription-only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.

Important potential risks

Risk	What is known
Theoretical risk of antibody production (immunogenicity) which may result in a lack of effect	As with all large therapeutic proteins, there is a theoretical risk that the body may produce antibodies against the medicine that result in a lack of effect. Study FIN3001 showed similar immunogenicity results for both Bemfola and Gonal-f groups.
Breast cancer	The SmPCs for Bemfola and Gonal-f contain the following warning: "*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".*
Other reproductive system cancers (e.g. ovarian cancer, cervical cancer)	The SmPCs for Bemfola and Gonal-f contain the following warning: "*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".*
Ectopic pregnancy (pregnancy that occurs outside the womb)	The SmPCs for Bemfola and Gonal-f contain the following warning: "*Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART was reported to be higher than in the general population".*
Congenital abnormalities	The SmPCs for Bemfola and Gonal-f contain the following warning: "*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*

Risk	What is known
	characteristics) and multiple pregnancies".

Missing information

Risk	What is known
Use in female patients >40 years of age	Bemfola has only been tested in females <40 years of age. The reference product Gonal-f has been used in women >40 years of age without identification of any safety risks. Given that similarity between Bemfola and Gonal-f has been established, Bemfola can also be used in women >40 years of age. An ongoing phase-3 study will provide additional data for females aged between 35 and 42 years.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for X can be found on Bemfola's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Phase III investigator and assessor-blinded 1:1 randomized parallel group multi-center study	Compare efficacy and safety of 2 recombinant-human FSH formulations (Bemfola pen vs. Gonal-f RFF pen) in normal ovulatory women 35 to 42 years of age undergoing IVF.	Collect additional data to compare the risk of OHSS between Bemfola and the reference product.	Started	21 April 2016 (final Clinical Study Report)

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 02-2014.