Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
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follitropin alfa 75 units, 150 units, 225 units, 300 units, 450 units pre-filled pen for subcutaneous injection (Bemfola®) SMC No. (1025/15)

FINOX Biotech

09 January 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

follitropin alfa (Bemfola®) is accepted for use within NHS Scotland.

Indication under review:
In adult women for:

- anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.
- stimulation of multi-follicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer.
- in association with a luteinising hormone (LH) preparation for the stimulation of follicular development in women with severe LH and follicle-stimulating hormone (FSH) deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 units/L.

In adult men for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotrophin (hCG) therapy.

Follitropin alfa (Bemfola®) is a biosimilar that has demonstrated clinical equivalence to another follitropin alfa product for stimulation of multi-follicular development for superovulation in ART. The British National Formulary advises that it is good practice to prescribe biological medicinal products by brand name.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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In adult men for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotrophin (hCG) therapy.

Dosing Information

See summary of product characteristics

Product availability date

September 2014

Summary of evidence on comparative efficacy

Follitropin alfa (Bemfola®) is a biosimilar of follitropin alfa (Gonal-f®), which is recombinant human follicle stimulating hormone (r-hFSH). European Medicines Agency (EMA) guidance notes that demonstration of similar efficacy and safety of the r-hFSH product to the reference product for stimulation of multi-follicular development in patients undergoing superovulation for assisted reproductive technology (ART) will allow extrapolation to other therapeutic indications approved for the reference product.[1] Follitropin alfa (Bemfola®) is licensed for all the indications of the reference product, follitropin alfa (Gonal-f®).[2,3]

In a phase III assessor-blinded study (FIN3001), women aged 20 to 38 years, who were undergoing stimulation of multi-follicular development for superovulation for ART, had their endogenous FSH production down-regulated with a gonadotrophin-releasing hormone (GnRH) agonist and were randomised in a 2:1 ratio to follitropin alfa (Bemfola®) or follitropin alfa (Gonal-f®), both at a starting dose of 150 units subcutaneous injection daily.[4] Treatment was continued for up to 16 days until one follicle reached a diameter of at least 18mm and two further follicles reached a diameter of at least 16mm. At this point, human chorionic gonadotrophin (hCG) was administered to trigger ovulation.[4] Oocytes were removed and intracytoplasmic sperm injection (ICSI) or in vitro fertilisation (IVF) was performed according to standard techniques. A maximum of two embryos were transferred 2 to 5 days after oocyte retrieval.[5] The primary outcome was the number of oocytes retrieved. It was pre-specified that clinical equivalence would be demonstrated if the mean difference between the number of oocytes retrieved from each treatment group was less than 3.[4]

Although 410 patients were randomised to the study, due to Good Clinical Practice (GCP) issues at one centre, patients enrolled at this UK site were excluded from the study.[4] In the per-protocol (PP) population, which included 249 patients in the follitropin alfa (Bemfola®) group and 123 patients in the follitropin alfa (Gonal-f®) group, the mean (standard deviation) number of oocytes retrieved was 10.8 (5.11) and 10.6 (6.06) in the follitropin alfa (Bemfola®) and follitropin alfa (Gonal-f®) groups, respectively, with a between treatment group difference of 0.27 (95% CI: -1.34 to 1.32). Therefore, clinical equivalence of follitropin alfa (Bemfola®) to follitropin alfa (Gonal-f®) was demonstrated. Similar results were reported in the full analysis set (FAS).[4]

Summary of evidence on comparative safety

The adverse effect profile of follitropin alfa (Bemfola®) is similar to that of the reference product follitropin alfa (Gonal-f®). In the phase III study 73% (182/249) and 67% (83/123) of patients in the respective groups had an adverse event, which was considered to be related to study medication in 64% (160/249) and 54% (66/123). The most common adverse events were injection site reactions and adverse events on the reproductive system, with ovarian hyperstimulation syndrome (OHSS) reported by more patients in the follitropin alfa (Bemfola®) group, 22% versus 13%. The majority of these were mild to moderate.[4] Symptoms of mild OHSS include transient lower abdominal discomfort, nausea, vomiting, diarrhoea, or abdominal distension, typically occurring soon after ovulation (in superovulation cycles) or after oocyte retrieval (in ART cycles), but possibly delayed. Moderate symptoms are the same but persist, worsen, or include ascites.[5,6] It has been suggested that differences in patients' attitudes to reporting of adverse events for experimental versus established medicines may have influenced this.[4,5]

Summary of clinical effectiveness issues

Follitropin alfa (Bemfola®) is a biosimilar of follitropin alfa (Gonal-f®). Follitropin alfa (Gonal-f®) has not been reviewed by SMC as it was licensed before 2002. It is used for stimulation of follicular development in women undergoing ART or who have anovulation or hormone (LH and FSH) deficiency and, in combination with hCG, for stimulation of spermatogenesis in men with hypogonadotropic hypogonadism.

In a direct comparative study, clinical equivalence of follitropin alfa (Bemfola®) to the reference product, follitropin alfa (Gonal-f®), was demonstrated in terms of number of oocytes retrieved during stimulation of multi-follicular development in patients undergoing superovulation for ART.[4] This is the model recommended by the EMA for demonstration of clinical equivalence in r-hFSH products. Extrapolation of clinical equivalence to the other indications of the reference product, follitropin alfa (Gonal-f®), followed in accordance with regulatory guidance. Therefore, there are no clinical data for several of the indications for which follitropin alfa (Bemfola®) is approved.

Follitropin alfa (Bemfola®) was associated with higher incidences of adverse events compared to follitropin alfa (Gonal-f®), in particular OHSS. In this study, only ultrasound assessors were blinded to treatment allocation. The partially unblinded nature of the study may have affected reporting of subjective outcomes, such as adverse events. The extent to which this explains the differences in adverse events is unclear.

There was a high withdrawal rate from the phase III study for reasons classified as “other”. Most of these were failure to become pregnant, with rates comparable between the groups.[5]

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing follitropin alfa (Bemfola®) with the reference product of follitropin alfa (Gonal-f®) in patients undergoing superovulation for ART procedures such as IVF. The doses used for other clinical indications included in the licence were considered in the sensitivity analysis. The time horizon of the analysis was one cycle of infertility treatment.

The clinical data to support comparable efficacy were taken from the pivotal study described above. Only drug costs were included in the analysis. The base case analysis used the doses from the pivotal study where patients in both arms required 21 of the 75unit doses per cycle.

The total cost of one cycle of follitropin alfa (Bemfola®) was estimated to be £493.50, which is the same as the cost per cycle of the reference product follitropin alfa (Gonal-f®).

The results were also presented based on the recommended doses for each of the different patient groups covered by the licensed indications. The results of this analysis are presented in the table below.

Indications	**follitropin alfa (Bemfola®) total cost per cycle**	**follitropin alfa (Gonal-f®) total cost of per cycle**	**Cost-minimisation analysis results**
Woman with anovulation	£164.50 - £658.00	£164.50 - £658.00	Cost neutral
Woman with low LH and FSH levels	£164.50 - £658.00	£164.50 - £658.00	Cost neutral
Men with congenital or acquired hypogonadotrophic hypogonadism	£2,444.00	£2,444.00	Cost neutral

The following limitations were noted:

- The costs of follitropin alfa (Gonal-f®) are based on the assumption that only the 300 units and 900 units prefilled pen formulations of are used in practice in Scotland. Other formulations of follitropin alfa (Gonal-f®) are available at a slightly lower drug cost, but would also be associated with an additional administration cost and, therefore, it is likely that follitropin alfa (Bemfola®) would remain a cost-effective treatment option overall.
- As with other biosimilar medicines assessed by SMC, there is a lack of clinical data comparing follitropin alfa (Bemfola®) with the reference product across the range of indications. However, it is acknowledged that this is not required for licensing purposes as the conclusion of equivalence is assumed to extrapolate to the other indications covered by the reference product.

The analysis showed follitropin alfa (Bemfola®) is clinically equivalent to follitropin alfa (Gonal-f®) and, based on the 300 unit and 900 unit formulations, is available at the same drug cost. As such, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group Submission was not made.

Additional information: guidelines and protocols

In February 2013 the National Institute of Health and Care Excellence (NICE) published clinical guideline number 156; fertility: assessment and treatment of people with fertility problems. This recommends use of ovarian stimulation as part of IVF treatment and the use of either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. The guideline also recommends when using gonadotrophins for ovarian stimulation in IVF treatment use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as: age; BMI; presence of polycystic ovaries; and ovarian reserve. Do not use a dosage of follicle-stimulating hormone of more than 450 units/day. Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation. It also recommends that men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility. Also, offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference: laparoscopic ovarian drilling; combined treatment with clomifene citrate and metformin if not already offered as first-line treatment or gonadotrophins. Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment. Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation.[7]

Additional information: comparators

Follitropin alfa (Bemfola®) is a biosimilar of follitropin alfa (Gonal-f®) and is likely to be used in place of this in practice.

Cost of relevant comparators

Drug	Dose Regimen	Cost per day (£)*
Follitropin alfa (Bemfola®) pen	**75 units to 450 units sc daily**	**24 to 141**
Follitropin alfa (Gonal-f®) pen	75 units to 450 units sc daily	24 to 141
Follitropin alfa (Gonal-f®) vials	75 units to 450 units sc daily	21 to 126

Doses are for general comparison and do not imply therapeutic equivalence. Costs for Gonal-f® from eVadis on 3 November 2014 and for Bemfola® from eMIMS on 10 November 2014. *duration of treatment course varies depending on indication.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 4,298 in year 1 and 5,087 in year 5 with an estimated uptake rate of 4% in year 1 rising to 25% in year 5. The patient numbers were estimated based on all indications covered by the licence.

Based on the lowest dose, the gross medicines budget impact was estimated to be £57k in year 1 and £423k in year 5. Using the highest dose, the gross medicines budget impact was estimated to be £304k in year 1 and £2.25m in year 5. As other medicines are assumed to be displaced, the net medicines budget impact was estimated to be cost-neutral in both scenarios.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH). February 2013.
2. Follitropin alfa 150 IU/0.25mL pre-filled pen (Bemfola®) summary of product characteristics. Finox Biotech. European Medicines Agency www.ema.europa.eu. Last accessed 3 November 2014.
3. Follitropin alfa 300 IU pen (Gonal-f®) summary of product characteristics. Merck Serono. Electronic Medicines Compendium www.medicines.org.uk Last updated 12 May 2014
4. European Medicines Agency. European Public Assessment Report. Bemfola (follitropin alfa). 26/06/14, EMEA/H/C/002615. www.ema.europa.eu
5. Finox Biotech (data on file). Clincal study report for FIN3001. A Phase III assessor-blinded randomised parallel group multi-centre study to compare efficacy and safety of two r-hFSH formulations (AFOLIA vs Gonal-f®) in women for assisted reproductive treatment, September 2012
6. The Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimilation syndrome. Fertil Steril 2008;90:S188-93.
7. National Institute for Health and Care Excellence. Clinical guideline number 156. Fertility: assessment and treatment for people with fertility problems, February 2013.

This assessment is based on data submitted by the applicant company up to and including 10 November 2014.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.