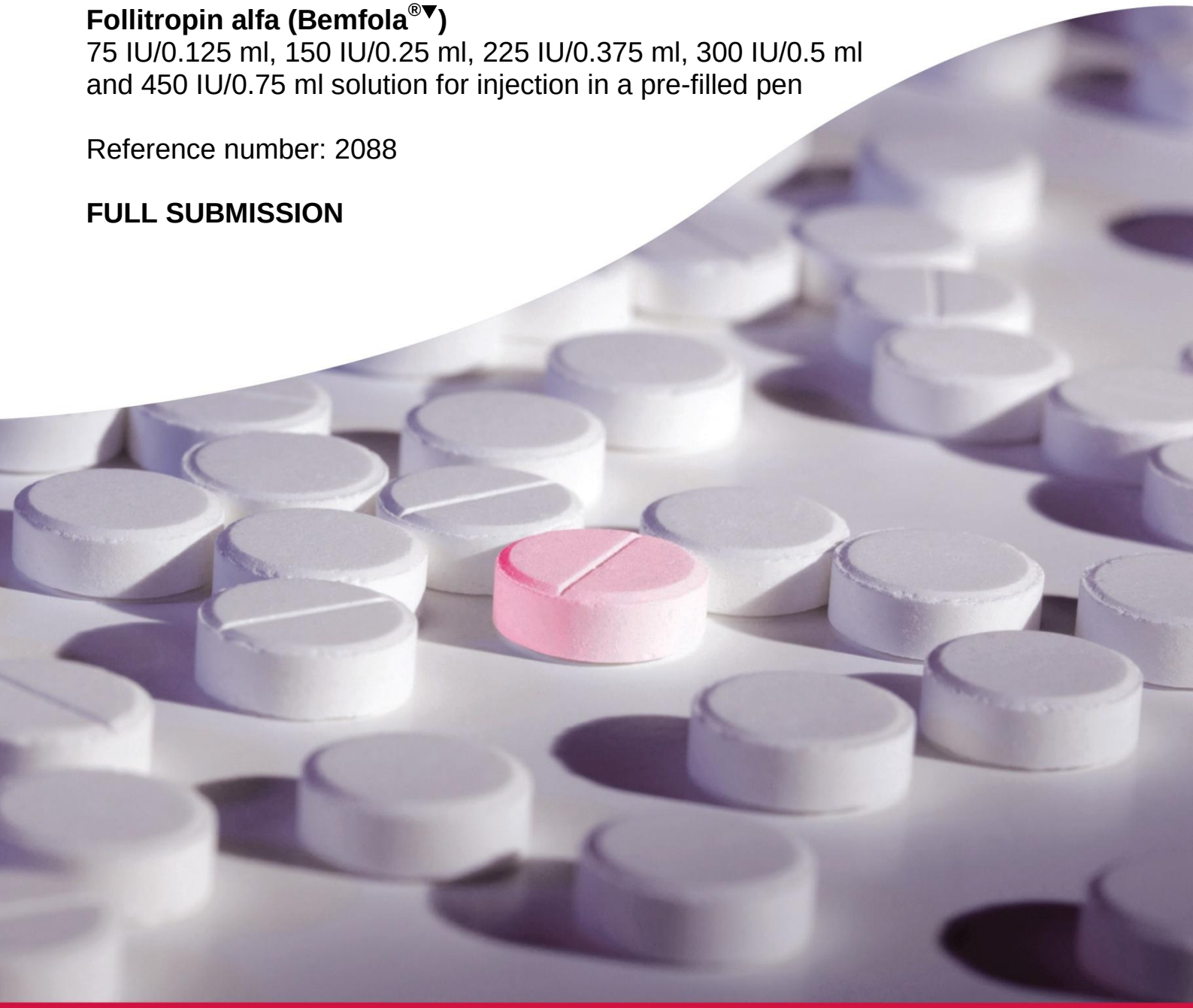
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Follitropin alfa (Bemfola®▼)
75 IU/0.125 ml, 150 IU/0.25 ml, 225 IU/0.375 ml, 300 IU/0.5 ml and 450 IU/0.75 ml solution for injection in a pre-filled pen

Reference number: 2088

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Follitropin alfa (Bemfola®▼) 75 IU/0.125 ml, 150 IU/0.25 ml, 225 IU/0.375 ml, 300 IU/0.5 ml and 450 IU/0.75 ml solution for injection in a pre-filled pen

This assessment report is based on evidence submitted by FINOX Biotech on 28 August 2014[1].

1.0 PRODUCT DETAILS

Licensed indications under consideration	Follitropin alfa (Bemfola®▼) is indicated for: In adult women • Anovulation (including polycystic ovarian disease, PCOD) 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 • For the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.
Dosing	The commonly used dosing regimen for women with anovulation (including PCOD) commences at 75–150 IU of Bemfola®▼ 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. The commonly used regimen for superovulation involves the administration of 150–225 IU of Bemfola®▼ daily commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved, with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In LH and FSH deficient women, Bemfola®▼ should be given as a course of daily injections simultaneously with lutropin alfa. The 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 oestrogen response. In men with hypogonadotrophic 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.

	Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	27 March 2014[3]

2.0 DECISION CONTEXT

2.1 Background

Approximately one in seven heterosexual couples in the UK are affected by infertility (defined as the failure to conceive after one year of unprotected sexual intercourse)[4]. The most common causes of infertility are: male infertility; ovulatory disorders; tubal disorders as well as unexplained infertility, and as a result, a greater proportion of infertile couples are seeking help for such problems[4,5]. For these couples, there are three types of treatment available:

- Medical treatment to restore fertility (for example, the use of medicines for ovulation stimulation);
- Surgical treatment to restore fertility (for example, a laparoscopy procedure for the ablation of endometriosis);
- Assisted reproduction techniques (ART) such as in vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI)[4].

Follicle-stimulating hormone (FSH) is naturally produced in the body by the pituitary gland, and plays a significant role in regulating reproductive function in both males and females[6]. Exogenous FSH is administered to stimulate multifollicular development in women undergoing ART, to induce ovulation in women with anovulatory infertility and for the induction and maintenance of spermatogenesis in men[6]. Bemfola®▼ is a European-Medicines Agency (EMA)-approved biosimilar medicinal product, i.e. a medicine that has been demonstrated to be similar in quality, safety and efficacy to the biological reference product Gonal-f®[1,2]. Both Bemfola®▼ and Gonal-f® contain the active substance follitropin alfa. Follitropin alfa is a recombinant human FSH (r-hFSH) that is produced by a method known as 'recombinant DNA technology'[7].

2.2 Comparators

The comparator included in the company submission was Gonal-f®[1].

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Clinical Guideline (CG) 156. Fertility: assessment and treatment for people with fertility problems (2013)[4].
- EMA. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH; 2013)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

EMA guidelines state that a biosimilar medicine should demonstrate comparable quality, efficacy and safety to its reference product[8]. Therefore, if Bemfola®▼ is demonstrated to have comparable quality, efficacy and safety to that of its reference product, Gonal-f®, for the stimulation of multifollicular development in patients undergoing superovulation for ART then the extrapolation of data from one indication to another is permitted[6].

In support of the use of Bemfola®▼ for the indications under consideration, the applicant company have provided data from the pivotal trial, FIN3001. The company also included a brief overview of the FIN1001 trial which demonstrated the equivalence of pharmacokinetics of Bemfola®▼ and Gonal-f® in healthy women; however, this study will not be discussed further[1].

3.1 FIN3001

This was a randomised, assessor-blinded, parallel group, multicentre phase III trial. This study compared the efficacy and safety of Bemfola®▼ and Gonal-f® in female patients undergoing ART via IVF or ICSI. Gonal-f® was chosen as it is the biological reference product for Bemfola®▼, and is the standard of care in the European countries where this study was conducted. The majority of patients were Caucasian with a mean age of < 35 years and had a duration of infertility of 3.1 years.

All participating patients (n = 372) responded to an injection of gonadotrophin-releasing hormone (GnRH) agonist and were therefore randomised in a 2:1 ratio to receive a fixed subcutaneous daily dose of 150 IU of either Bemfola®▼ (n = 249) or Gonal-f® (n = 123). The first dose of the study medicine was self-administered under the supervision of the study nurse and all following doses were self-administered without supervision[1]. Daily treatment continued for at least six days and was maintained for a maximum of 16 days unless the patient was at risk of imminent ovarian hyperstimulation syndrome (OHSS)[1,7]. Ovulation occurred between 34–36 hours after human chorionic gonadotrophin (hCG) administration and oocytes were retrieved according to standard techniques of the investigating centres in preparation for IVF or ICSI[1,7].

The primary efficacy endpoint showed no significant differences in the mean number of oocytes retrieved between the treatment groups. Equivalence between Bemfola®▼ and Gonal-f® was demonstrated as the mean difference between the numbers of oocytes retrieved was less than 3 (with a standard deviation of 7.06) (see Table 1). Secondary efficacy endpoint analyses, which focussed on the quality of the oocytes retrieved along with the analysis of other clinically relevant outcomes, i.e. fertilisation rate, clinical pregnancy rate and pharmacodynamic parameters all demonstrated no significant difference[1,7].

Table 1. Overview of primary efficacy endpoints from the FIN3001 study[1,7]

	FAS population		PP population	
	Bemfola®▼ (n = 246)	Gonal-f® (n = 123)	Bemfola®▼ (n = 220)	Gonal-f® (n = 113)
Treatment cycle 1:				
Mean number of oocytes retrieved	10.7	10.4	10.8	10.6
Standard deviation	± 5.62	± 6.14	± 5.11	± 6.06
Treatment difference	0.29 (95 % CI: −1.29, 1.34) p = 0.0003		0.27 (95 % CI: −1.34, 1.32) p = 0.0003	

CI: confidence interval; FAS: full analysis set (patients who received at least one dose of the study treatment according to the protocol); PP: per protocol set (patients who completed the study according to the protocol).

3.1.1 FIN3001 addendum study

Patients who were unsuccessful after the first treatment cycle (cycle 1) were entered into an addendum study which aimed to assess the immunogenicity and safety of Bemfola®▼ in a second treatment cycle (cycle 2). The patients remained in their allocated treatment groups (Bemfola®▼: n = 72; Gonal-f®: n = 38) and followed the same procedure as that used for cycle 1. Cycle 2 had the same primary and secondary efficacy endpoints as cycle 1; the results were found to be in support of biosimilarity[1,7].

3.2 Comparative safety

In the safety analysis set (SAS: comprising all randomised patients having received one administration of the study treatment; n = 372), safety and tolerability were evaluated by observed and reported treatment-emergent adverse events (TEAEs). The most common study-medicine related TEAEs reported in the Bemfola®▼ and Gonal-f® treatment groups were: injection site erythema (23.7% versus 28.5%), OHSS (22.1% versus 13.0%), injection site haematoma (20.9 % versus 10.6%) and headache (20.9% versus 17.9%)[1,7]. Treatment differences in the incidence of individual events were reported for OHSS (9% more frequent in the Bemfola®▼ treatment group) and injection site haematoma (10% more frequent in the Bemfola®▼ treatment group)[7]. The occurrence of serious AEs (SAEs) was higher in the Bemfola®▼ treatment group when compared to the Gonal-f® treatment group (4.4% versus 2.4%)[7]. The frequencies of medicine-related AEs resulting in permanent withdrawal from the study were not balanced between the two treatment groups (ten patients [4.0%] in the Bemfola®▼ treatment group and one patient [0.8%] in the Gonal-f® treatment group). This difference was mainly due to an increase in the incidence of OHSS (3.6% versus 0.8%). All cases of OHSS were considered to be of moderate severity except for one case in the Bemfola®▼ group which was considered to be of mild severity. No deaths were reported in either treatment group[1,7].

3.3 AWTTC critique

- The Committee for Medicinal Products for Human Use (CHMP) concluded that Bemfola®▼ can be considered biosimilar to Gonal-f®. The pivotal FIN3001 trial was acceptable and in accordance with EMA guidelines, which state that 'clinical comparability regarding efficacy between the similar and the reference biological medicinal product should be demonstrated in an adequately powered, randomised, parallel group clinical trial'[6,7]
- The patients participating in the pivotal FIN3001 trial were already undergoing stimulation of multifollicular development[1]; however, it is unclear as to what medicines the patients were taking for this.
- The higher incidence of OHSS and the discontinuation due to OHSS were both noted by CHMP. However, CHMP accepted these differences between treatment arms based on the company's explanation that the higher proportion of Anti-Müllerian hormone (AMH) levels (≥ 24 pmol/l) in the baseline characteristics of the Bemfola®▼ group could have contributed to this higher OHSS incidence in this treatment group. Further, dissimilarities in dose reduction were observed between the Bemfola®▼ and Gonal-f® groups, which also could have resulted in a higher incidence of OHSS for Bemfola®▼[7].
- The applicant company state that Bemfola®▼ is only available at a specific IU and this would eliminate any patient error in dosage that could be realised with a pre-filled pen device of alterable IU as can be the case with the biological medicinal reference product[1]. However, CHMP state that the administration of Bemfola®▼ may become inconvenient when incremental increases in dose are required. For example, if a patient is using the 150 IU pen and needs to increase the dose, another pen would be required; whereas with the 900 IU Gonal-f® pen this would not be an issue as multiple different doses can be administered with the same pen within 28 days of opening. Although, specific IU can reduce patient error in dosage, the potential need of increased doses and thus the use of multiple pens could potentially increase patient error[7].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes cost minimisation analyses (CMAs) of Bemfola®▼ compared with Gonal-f® within its licensed indications[1].

The company has adopted a CMA approach on the basis of the phase III FIN3001 trial, which demonstrated the equivalence of Bemfola®▼ versus Gonal-f® for the primary endpoint of number of oocytes retrieved in women undergoing ART, and comparable effects on a wide range of secondary endpoints and AEs[7]. Demonstration of biosimilarity in this key patient population is considered by the regulatory authority to allow extrapolation to other therapeutic indications approved for the reference product[6].

The company note that the mean dose and duration of treatment in the FIN3001 trial was similar for Bemfola®▼ (1555.7 IU over 10.6 days) and Gonal-f® (1569.2 IU over 10.7 days), and estimate that delivery of these cumulative doses would require 21 x 75 IU equivalent doses[1]. Based on current prices, the company has estimated the cost per 75 IU dose equivalent to be £23.50 for both Bemfola®▼ (company pricing information across all presentations of its single use pens) and Gonal-f® (assuming the use of pre-filled multidose pens)[9].

4.1.2 Results

On this basis of the above, the company estimates the cost of Bemfola®▼ to be the same as for Gonal-f® at equivalent doses in all indications.

4.1.3 AWTTC critique

The CMA approach assumes equivalence in all domains of health outcomes. The EMA considered that therapeutic equivalence for the primary endpoint had been met and that secondary endpoints and adverse event rates were compatible with the biosimilarity of Bemfola®▼ and Gonal-f®[7]. However, it should be noted that Bemfola®▼ is available only as single use, fixed dose, pre-filled pens, in contrast to Gonal-f®, which is available as multidose vials and pre-filled pens. The company's CMA assumes all doses of Bemfola®▼ are in multiples of 75 IU.

The company suggests that the single dose presentation of Bemfola®▼ may reduce the potential for dosing errors compared with multidose presentations of Gonal-f® [commercial in confidence information removed][1]. As doses need to be individually tailored to response, it is not possible to determine the impact of potential dose wastage on costs arising from use of the different presentations; however, on a fixed dose basis Bemfola®▼ would be cost neutral with Gonal-f®.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost effectiveness analyses of Bemfola®▼ of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company's budget impact analysis relates only to use in IVF. Based on data from the Human Fertilisation Embryology Authority (HFEA), a total of 1,351 women underwent IVF treatment and received a total of 1,732 cycles of IVF treatment in Wales in 2011[11], averaging 1.28 cycles per woman. In addition, the number of IVF cycles

increased by 4.3% from 2010–11 in the UK[12]. By extrapolation of these figures, the company estimates that 1,533 women in Wales will undergo IVF treatment in 2014 (receiving a total of 1,965 cycles), increasing to 1,814 women (receiving 2,326 cycles) in 2018[1].

The company estimates that Bemfola®▼ will take a patient share of 4% in Wales in 2014, increasing to 25% in 2018. This patient share is expected to be taken predominantly from Gonal-f®. The same dose and duration of treatment for both Bemfola®▼ and Gonal-f®, as was observed in the FIN3001 trial (21 x 75 IU equivalent doses), is assumed.

5.1.2 Results

Assuming an average of 1.28 cycles per woman, the company estimates the cost per patient per year to be £633 with either Bemfola®▼ or Gonal-f®. The introduction of Bemfola®▼ is therefore estimated to be cost neutral.

The company has explored scenarios of a change in the required dose of Bemfola®▼ in the range of ±25%, whilst assuming no change in the required dose of Gonal-f®. As would be expected, a 25% increase (to 1944.6 IU) in Bemfola®▼ dose would result in the need for 26 x 75 IU dose equivalents of Bemfola®▼ at a total cost of £611 per cycle, resulting in an increased cost per cycle of £117.50 compared to Gonal-f®. A 25% reduction in Bemfola®▼ dose (to 1166.8 IU) would result in the need for 16 x 75 IU dose equivalents at a total Bemfola®▼ cost of £376 per cycle, resulting in a cost-saving per cycle of £117.50 when compared to Gonal-f®[1].

5.1.3 AWTTC critique

- The company's budget impact analysis assumes use only in IVF and does not consider alternative licensed uses of Bemfola®▼. However, irrespective of the actual number of patients receiving NHS-funded Bemfola®▼, on a fixed dose basis and at price parity, cost neutrality versus Gonal-F® is anticipated.
- The scenario analyses are of unclear informative value, as no basis for assuming such a substantial difference in required doses between the biosimilar formulations of Bemfola®▼ is provided and the key trial demonstrating equivalence found no such discrepancy.

5.2 Comparative unit costs

Table 2 includes comparative acquisition costs for Gonal-f® and the biosimilar Bemfola®▼, based on BNF list prices[9] and company information[1]. As doses need to be individually tailored and vary by licensed indication, only the acquisition costs for the different presentations are provided.

Table 2. Comparative acquisition costs for Gonal-f® and the biosimilar Bemfola®▼

Medicine	Dose	List price*
Gonal-f®	75 IU ampoule	£21.02
	0.75 ml (450 IU) multidose vial	£126.10
	1.75 ml (1050 IU) multidose vial	£294.22
	0.5 ml (300 IU) pre-filled, multidose pen	£94.00
	0.75 ml (450 IU) pre-filled, multidose pen	£141.00
	1.5 ml (900 IU) pre-filled, multidose pen	£282.00
Bemfola®▼	75 IU pre-filled, single use syringe	£23.50
	150 IU pre-filled, single use syringe	£47.00
	225 IU pre-filled, single use syringe	£70.50
	300 IU pre-filled, single use syringe	£94.00
	450 IU pre-filled, single use syringe	£141.00

*Price of Gonal-f® based on British National Formulary (BNF) list prices as of 3 September 2014[9]. Bemfola®▼ price based on company information[1].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, follitropin alfa (Bemfola®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that follitropin alfa (Bemfola®▼) will be supplied by a home healthcare provider.

6.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.3 Evidence search

Date of evidence search: 28 April 2014
Date range of evidence search: No date limits were applied to database searches.

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