Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Corifollitropin alfa

Proprietary Product Name: Elonva

Sponsor: Schering-Plough Pty Ltd

November 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity (NCE)
Decision:	Approved
Date of Decision:	21 July 2010
Active ingredient(s):	Corifollitropin alfa
Product Name(s):	Elonva
Sponsor's Name and Address:	Schering-Plough Pty Ltd Level 4, 66 Waterloo Rd, North Ryde, NSW 2113
Dose form(s):	Solution for injection
Strength(s):	100µg/0.5mL and 150µg/0.5mL
Container(s):	Prefilled syringes
Pack size(s):	1 syringe per pack
Approved Therapeutic use:	Controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing *in-vitro* fertilisation techniques.
Route(s) of administration:	Subcutaneous injection (SC)
Dosage:	Single injection (100µg for≤60kg and 150µ g for >60kg) during early follicular phase.
ARTG number(s):	160646 and 160645

Product Background

Corifollitropin alfa is a molecular analogue of follicle-stimulating hormone (FSH), produced in Chinese Hamster Ovary (CHO) using recombinant DNA techniques. Like native glycoprotein hormones, the recombinant product is composed of a species-specific alpha subunit and a hormone specific beta subunit. That is, corifollitropin alfa consists of recombinant human FSH (rFSH), in which the alpha subunit is identical with that of human FSH but with a C-terminal extension on the beta subunit. The amino acid extension (derived from hCG) prolongs absorption and increases the terminal elimination half-life of FSH, making it a more long acting therapeutic substance. Thus, it is designed as a sustained follicle stimulant with the same pharmacodynamic profile as follitropin beta (rFSH, trade name Puregon®, also marketed by Schering-Plough), but with a extended elimination half life.

The application is to register corifollitropin alfa as a single injection designed to provide FSH stimulation of follicular development over the first seven days of a COS cycle, as an alternative to daily injections of rFSH. Gonal-f and Puregon® are recombinant FSH products currently registered in Australia for similar indications. The treatment is offered in the sense of it being more convenient and less invasive. There is no claim that it is superior to the existing daily FSH injection regimen in terms of treatment outcomes or safety.

Regulatory Status

As of 19 April 2010, a similar application has been approved in the European Union (EU) on 25 January 2010. There were no referrals, withdrawals or rejections recorded. The approved indication in the EU, Iceland and Norway is as follows:

> Controlled ovarian stimulation (COS) in combination with GnRH antagonists for the development of multiple follicles in women participating in Assisted Reproductive Technology (ART) program.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure

The α-subunit is identical with that of all gonadotropins and the β-subunit has been genetically engineered to consist of the complete β-subunit of follicle stimulating hormone extended with the C-terminal peptide of the β-subunit of hCG.

Manufacture

A cDNA/gene hybrid for the gonadotropin α-subunit together with FSH β-subunit gene extended by the C-terminal peptide of hCG was inserted in the plasmid under the control of a promoter with promoter enhancer sequences. This was transfected into the CHO-K1 cell-line. The cell-line has been suitably characterised and is stable. Cell banking processes are satisfactory. All viral/prion safety issues have been satisfactorily addressed. The cells are cultured in fermentors with satisfactory in-process controls. The medium is purified by six chromatography, four filtration steps and two viral removal/inactivation steps. Once again, the in-process controls are appropriate and process adequately validated. Batch analysis shows satisfactory consistency of manufacture.

Physical and Chemical Properties

The primary structure of the substance was confirmed with respect to molecular mass, amino acid composition and sequence and disulphide bonding. Consistent higher order structure was demonstrated immunologically and with ultraviolet (UV)/visual (Vis) spectroscopy, circular dichroism, fluorescence, nuclear magnetic resonance spectroscopy, and analytical ultracentrifugation. Post-translational modification especially N- and O-glycosylation was shown to be acceptable. Process- and product-derived impurities were shown to be at acceptable levels and/or adequately controlled.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use have been supported by appropriate validation data.

Stability

Stability data have been generated under real time conditions to characterise the stability/ degradation profile of the substance and to establish a shelf life of 24 months at -20°C (with short excursions to no more than 25°C)

Drug Product

Formulation(s)

Elonva is a solution for injection containing corifollitropin alfa at strengths of 100µg/0.5mL and 150µg/0.5mL in 1mL prefilled syringes with rubber plungers and tip caps. These syringes are supplied in a single syringe pack. The components are: corifollitropin alfa (active ingredient), sodium citrate dihydrate, sucrose, L-methionine, Polysorbate 20, sodium hydroxide, hydrochloric acid and water.

Manufacture

The product is manufactured by formulation and filling under aseptic conditions followed by sterilisation using 2-step filtration.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, are supported by appropriate validation data.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is not photostable.

The proposed shelf life is 24 months at 2-8°C in the dark with excursions to <30°C of no more than 30 days. In-use stability data have also been submitted. As the solution does not contain a preservative, it is for single use only and should be used immediately upon opening.

Biopharmaceutics

Two bioavailability studies (Studies 38803 and 33823) were submitted in support of the application. These are summarised below.

Rate and extent of absorption

- The absolute bioavailability of corifollitropin alfa after subcutaneous administration is 58 %.
- Time to maximum plasma concentration (T_{max}) after SC injections is approximately 44 hours.
- Maximum plasma concentration (C_{max}) is about 3.1 ng/mL after a single SC dose of 100 µg.
- The half-life ($t_{1/2}$) of corifollitropin alfa after subcutaneous administration is 69 hours.
- The clearance of corifollitropin alfa is 0.13 L/h.
- The volume of distribution at equilibrium (Vss) is 9.2 L.
- The initial volume of distribution (Vc) is 3.9 L.
- The terminal phase volume of distribution (Vz) is 12.3 L.

Metabolism, mode, route and rate of elimination

Body weight is a determinant of exposure to corifollitropin alfa. In clinical studies, serum concentrations of corifollitropin alfa were similar after administration of 100 micrograms corifollitropin alfa to women with a body weight < 60 kilograms and of 150 micrograms corifollitropin alfa to women with a body weight greater than 60 kilograms. Distribution, metabolism and elimination of corifollitropin alfa are very similar to other gonadotrophins, such as FSH, hCG and LH. After absorption into the blood, corifollitropin alfa is distributed mainly to

the ovaries and the kidneys. Elimination of corifollitropin alfa predominantly occurs via the kidneys.

***In-vivo* interconversion of enantiomers:** Not applicable.

Active entity(ies): Pharmacological activity resides with corifollitropin alfa**.**

Dose-response proportionality: The pharmacokinetic properties of corifollitropin alfa are independent of the administered dose over a dose wide range (7.5 to 240 micrograms).

Effects of food: Not applicable.

Effects of sex (if any): Not applicable.

Effects of genetic polymorphism (if any): No data available.

Labelling, packaging and documentation

The labelling has been evaluated and found acceptable.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no issues of concern.

III. Nonclinical Findings

Introduction

All studies relevant for this type of drug were submitted and were conducted and reported to satisfactory standards, with all main studies being Good Laboratory Practice (GLP) compliant. Some aspects (most notably, reproductive toxicity) were investigated in considerable detail. Studies submitted covered primary pharmacodynamics, secondary and safety pharmacology, pharmacokinetics, single dose toxicity in mice and rats, repeat dose toxicity in rats and dogs and reproductive toxicity (fertility and embryofetal toxicity) in rats and rabbits. Although not required for this type of drug, genotoxicity studies were also submitted. The quality of some of the earlier studies (mainly pharmacology studies) was lower than expected by today's standards, but some were repeated more recently.

The drug substance used in the majority of nonclinical studies was produced from cells cultured in the presence of fetal calf serum, insulin and transferrin. This differs from the manufacturing process proposed for the clinical drug substance, which is produced from cells grown in a protein-free medium. Chemical characterisation apparently revealed a small but significant glycosylation variation in corifollitropin alfa produced by the two manufacturing processes. The clinical form has more N-glycans, a slightly higher mean sialic acid occupation per glycan and a lower isoelectric point. In accordance with the European Medicines Agency (EMA) "*Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process*", bridging pharmacodynamic and pharmacokinetic studies were conducted to compare the two drug substances. There was no significant difference between the two drug substances in *in vitro* assays assessing signal transduction from the human FSH receptor and in *in vivo* bioactivity studies. The plasma half-life of the clinical (protein-free) drug substance was marginally but consistently higher than the non-protein free form. As exposures were determined based on area under curve (AUC), the toxicity profile of corifollitropin alfa produced in the presence of fetal calf serum would be expected to be indicative of the clinical drug substance.

Published nonclinical references cited in this part of the reported are listed in Appendix 1.

Pharmacology

Primary pharmacodynamics

Primary pharmacodynamic studies investigated *in vitro* receptor binding, signal transduction at the FSH receptor, activity in cultured follicles and oocytes, and *in vivo* activity. Receptor binding to the human FSH receptor was reported in three studies. In the two earlier studies (conducted in 1994 and 1996), corifollitropin alfa was reported to have lower (by about 36–46%) receptor binding affinity compared to rFSH. However, one study lacked methodological details and detailed results. In the other study, the results were shown for the log concentration response curves for corifollitropin alfa and rFSH, with rFSH showing greater binding per ng protein, but it was not clear how the relative binding affinity values were calculated. In the more recent Study (2007), corifollitropin alfa and rFSH were found to have comparable binding affinities for both the rat receptor and the human receptor (comparisons on a molar basis). Given the better quality of the 2007 report, its recent nature and the reproducibility of the recent findings, it seems likely that the binding affinity of corifollitropin alfa to the human FSH receptor is comparable to that of rFSH.

Several studies compared the *in vitro* signal transduction activity of corifollitropin alfa and rFSH at the human or rat FSH receptor. In these studies, the receptor was functionally coupled to adenylate cyclase, with measurements of cyclic adenosine monophosphate (cAMP) or cAMP-dependent stimulation of luciferase activity. Although both corifollitropin alfa and rFSH had similar binding kinetics at the FSH receptor, the *in vitro* signal transduction of corifollitropin alfa was consistently weaker (about 1.5–2 fold) than rFSH at both the human and rat receptors. This is not unprecedented as FSH variants having similar binding kinetics have been reported previously to have varying degrees of activation from the receptor (Zambrano *et al*., 1999).

Three *in vitro* models were used for testing the activity of corifollitropin alfa in stimulating ovarian follicle growth: mouse folliculogenesis, inhibition of apoptosis in rat antral follicles and the effect on resumption of meiosis in mouse oocytes. Corifollitropin alfa stimulated growth of mouse follicles at 30 mIU/mL (4.5 ng/mL, that is, similar to the C_{max} of 4.35 ng/mL at the maximum recommended human dose (MRHD)) compared with 100 mIU/mL (8.2 ng/mL) for rFSH, while both compounds stimulated oestradiol production (by the granulosa cells surrounding the oocyte within the follicle) at 100 mIU/mL (15 ng/mL for corifollitropin alfa and 8.2 ng/mL for rFSH).

Most ovarian follicles do not become ovulatory but undergo atresia by a hormone-controlled apoptotic process. Corifollitropin alfa failed to inhibit apoptosis in rat antral follicles grown in serum-free medium, but so too did one of the two batches of rFSH tested. In the resumption of meiosis model in mouse oocytes, corifollitropin alfa was approximately half as potent as rFSH when comparisons are made on a ng/mL basis. Overall, in the *in vitro* assays corifollitropin alfa demonstrated comparable potency to rFSH.

In vivo, corifollitropin alfa showed consistently higher potency than rFSH. In the standard Steelman Pohley assay (6 SC injections in rats over 3 successive days with sacrifice 2 days after the last injection); corifollitropin alfa was twice as potent in increasing ovarian weight as rFSH (in two separate studies). This greater potency of corifollitropin alfa *in vivo* is presumably due to its longer half life (in the rat, about 18 h for corifollitropin alfa compared with about 11 h for rFSH), and greater apparent accumulation after the multiple dosing schedule. In an adapted Steelman Pohley assay in which corifollitropin alfa and rFSH were administered only once, followed by sacrifice of the rats 72 h later, corifollitropin alfa also

showed greater potency than rFSH in increasing ovarian weight (about 1.6 fold), as well as in increasing serum oestradiol and progesterone, presumably again as a result of the longer half life of corifollitropin alfa and subsequent greater exposure.

In the superovulation assay, corifollitropin alfa again showed at least 2-fold greater potency than rFSH with respect to an increase in ovary weight, while it showed even greater (at least 4 fold) relative ovulatory potency (ova numbers) compared to rFSH, a characteristic of particular relevance to clinical use. Ova numbers reached a peak at a total dose of 0.5–1 µg/rat and then declined, probably due to ovarian overstimulation.

Although corifollitropin alfa showed higher potency than rFSH in the various *in vivo* assays, the maximum response was often similar. Thus, a maximum ovarian weight of about 200 mg was achieved in the Steelman Pohley assay (and for corifollitropin alfa in the adapted Steelman Pohley assay), a maximum number of ova of circa 30 was achieved in the superovulation assay, and the maximum concentration of progesterone achieved for corifollitropin alfa (250 nmol/L) was only slightly more than that for rFSH (225 nmol/L). Maximum oestradiol concentrations were not achieved with the doses used.

Secondary pharmacology

Although corifollitropin alfa contains the 28 amino acid carboxy terminal peptide (CTP) of hCG, a molecule that activates the LH receptor, no binding to, or bioactivity at the luteinising hormone (LH) receptor was observed at concentrations up to 15.15 µg/mL and 1.52 µg/mL, respectively. These concentrations are over 3000 times higher than the anticipated clinical C_{max} of 4.35 ng/mL. These data are consistent with the findings by Matzuk *et al*. (1990) that the CTP of hCG plays a minor role in LH receptor binding of the hCG molecule.

No signal transduction at the thyroid stimulating hormone (TSH) receptor was observed at concentrations up to 114 ng/mL (approximately 25 times the maximum serum corifollitropin alfa concentration at the MRHD). Therefore, the inclusion of the C-terminal extension on FSH in corifollitropin alfa does not appear to alter its specificity for the FSH receptor.

Corifollitropin alfa was also tested at concentrations up to 5 µg/mL (>1000 times the maximum serum corifollitropin alfa concentration at the MRHD) in a Novascreen assay and did not show any notable binding to any of the 41 receptors or ion channels tested.

Safety pharmacology

Safety pharmacology testing was limited to cardiovascular studies (one *in vitro* and one *in vivo)*. The sponsor argued that this was sufficient given that the general repeat-dose toxicity studies did not reveal any toxic effects of the drug to the central nervous system (CNS), respiratory or renal systems, and the lack of binding to a broad range of receptors or ion channels. This is considered acceptable for corifollitropin alfa, particularly in light of the available clinical experience with related products.

When tested at concentrations up to 5 µg/mL (>1000 times the maximum serum corifollitropin alfa concentration at the MRHD), corifollitropin alfa had no effect on hERG tail current in stably transfected HEK-293 cells. A single SC dose of 250 µg/kg corifollitropin alfa to male Beagle dogs had no effect on cardiovascular parameters, including electrocardiogram (ECG) intervals. This dose produced a C_{max} of 1313 ng/mL, 300 times the clinical C_{max}. Based on these findings, corifollitropin alfa is unlikely to have adverse cardiovascular effects.

Pharmacokinetics

The pharmacokinetics of corifollitropin alfa in all species investigated (human, rat and dog) were characterised by a relatively long half life ($t_{½}$ after a single SC administration of approximately 70 h in humans, 11–21 h in rats and 35–60 h in dogs), slow clearance (~2 mL/kg/h (for a 60 kg woman) in humans, 5 mL/kg/h in rats and 9 mL/kg/h in dogs), slow absorption after SC administration (T_{max} of approximately 44, 8 and 24 h in humans, rats and dogs, respectively) and a low volume of distribution (V_{ss} ~150 mL/kg for a 60 kg woman and 240 mL/kg in dogs and V_z ~110 mL/kg in rats). The pharmacokinetics was generally dose-linear in all species after both single and multiple doses and there was little evidence of a gender difference in any species. For all species, the half life of corifollitropin alfa following SC administration was ~1.5–2 fold higher than that of rFSH (approximately 70 h compared with 33 h in human, 20 h compared with 10 h in rats and 45 h compared with 30 h in dogs; rFSH values from Geurts *et al.*, 1996). The development of anti-corifollitropin alfa antibodies markedly reduced drug exposure in the laboratory animal species. Exposure after multiple dosing at 2 day intervals in animals that did not develop antibodies was about 1.5 times (rat) and 2 times (dog) that after a single dose. Bioavailability of a SC dose varied between species; 58% in humans, 45% in rats and 85% in dogs.

After a 20 µg/kg SC radioactive iodine (^{125}I)-corifollitropin alfa dose to female Wistar rats, the highest concentrations of radioactivity were found at the injection site, in blood, the ovaries and kidneys (as well as thyroid due to free ^{125}I following deiodination). The presence of high concentrations of radioactivity (at most time points throughout the experiment) at the injection site reflects the slow absorption of drug, while in the kidneys (and urinary bladder), it reflects the excretion of drug which is mainly by the urinary route. High concentrations of radioactivity in the ovaries reflect the site of action of corifollitropin alfa and presence of FSH receptor, while in the blood, it reflects the low distribution to the majority of organs/tissues (consistent with a low volume of distribution; about the physiological volume of blood plus extracellular fluid). Tissue distribution was similar in pigmented Lister hooded rats and albino Wistar rats, as were excretion profiles, thus providing no evidence for melanin binding. Distribution studies were only conducted in females, but in males a high concentration of radioactivity would be expected in the testes due to the presence of FSH receptors on Sertoli cells.

The tissue distribution/metabolism study in Wistar rats did not give any indication of breakdown products of corifollitropin alfa other than the α and β-subunits, which together with intact corifollitropin alfa, were the only bands observed upon sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE) of urine samples. A lack of obvious metabolic breakdown has been reported for endogenous FSH (Beitins *et al.*, 1977; human data for endogenous hormone).

The urinary route was the main route of excretion in both Wistar and Lister hooded rats, with 87% and 97% respectively of the administered dose (approximately 20 µg/kg SC) being excreted in urine over 168 h. This is consistent with the known role of the kidney in excretion of gonadotrophins, including FSH, in rats (Emmanouel *et al.*, 1984). The proposed Product Information recommends that Elonva is not used in patients with renal insufficiency, in whom the excretion of corifollitropin alfa might be impaired. Faecal excretion accounted for a small proportion of the administered dose (8–11%). Some excretion by the liver has been observed for gonadotrophins and probably takes place through the reticulo-endothelial system rather than via catabolism within hepatocytes (Nisula *et al.*, 1989).

Relative drug exposure

Relative drug exposures in the two pivotal repeat-dose toxicity studies are shown in the table below (Table 1). To be consistent with the use of mg in clinical studies, exposures that were originally determined on an IU basis have been converted to mg using the conversion factors provided by the sponsor. The human area under the concentration time-curves from time zero to infinity ($AUC_{0-\infty}$) represent exposure over 14 days and so exposure ratios have been calculated by multiplying the animal area under the concentration time-curves from time zero to 48 h ($AUC_{0-48\ h}$) values by 7 to cover a 14 day period. AUC and C_{max} data were from animals that did not develop antibodies and will therefore overestimate mean values for most groups.

Table 1.

Species (duration)	**Dose** (µg/kg/2 days)	**$AUC_{0-48\ h}$** (ng.h/mL)^	**C_{max}** (ng/mL)♦	**ER based on AUC***	**ER based on C_{max} #**
Rat (13 week)	1.64	154	38.4	1.6	9
	8.2	596	117	6	27
	41	nd	nd	nc	nc
Dog (13 week)	1.025	271	10.7	3	2
	2.87	607	75	6	17
	8.2	1900	222	20	51
Human	150 mg	668	4.35	–	–

^ data for day 76 (dogs)/78 (rats); dog data for females, rat data for males and females combined, human $AUC_{0-\infty}$;
♦data for day 76 (dogs)/78 (rats) for females; * Exposure ratio (ER) calculated as animal $AUC_{0-48\ h} \times 7$/human $AUC_{0-\infty}$; nd, inadequate data due to the antibody development; nc, not calculated.

The exposure ratios achieved in both the rat and dog are adequate, particularly given that the changes observed in the 13-week studies appear to be related to the primary pharmacological activity or to be secondary to increases in oestrogen and progesterone. Thus, the no observable effect level (NOEL) for toxicity other than that related directly or indirectly to primary pharmacological activity was the high dose (HD) in both species.

Toxicology

General toxicity

The rat and dog were the species used in the repeat-dose toxicity studies, while the mouse and rat were used in the single-dose toxicity studies. From the results of these toxicity studies and/or other evidence from primary pharmacodynamics studies, corifollitropin alfa was pharmacologically active in these species, as well as in rabbits (used in reproductive toxicity studies). This would be expected as the FSH receptor has high interspecies homology (85%, Ulloa-Aguirre *et al*., 2007).

Single-dose toxicity studies

Single dose toxicity studies were limited to one dose level administered by the IV and SC routes, 46 and 103 mg/kg, respectively. While there were no deaths in the rat study, two mortalities occurred in the mouse study following SC administration. The cause of death in one mouse was unclear, but the probable cause of death of the second mouse could be attributed to marked hepatocellular necrosis. The relationship of hepatic changes to treatment is unclear as 2/12 animals were affected, but no other toxicity studies were conducted in the

mouse and hepatic changes were not observed in toxicity studies conducted in other species. Most of the other changes observed in the single dose studies appeared to be related to the primary pharmacological activity of the drug and are discussed below in relation to the repeat-dose studies.

Repeat-dose toxicity studies

Duration of the repeat-dose toxicity studies in rats and dogs was acceptable and dose levels were appropriate; animal numbers, while acceptable, were relatively low, particularly for dogs. The repeated administration of corifollitropin alfa, a recombinant human protein, to these heterologous species induced the formation of anti-corifollitropin alfa antibodies, as would be expected for a foreign protein. This response, while not considered predictive of a similar response in humans, is important for interpreting the toxicity findings in the repeat dose studies.

In rats, antibody development was dose dependent and though antibody profile (titre time course) varied in individual animals, in most cases, high titres of neutralising antibodies were achieved. Rats with high titres had correspondingly low serum corifollitropin alfa levels, sometimes below the limit of quantification. Antibody development in dogs was less marked, with only a single male having a low titre and 5/8 females with detectable antibodies, two of which had high titres. As expected, serum concentrations of corifollitropin alfa negatively correlated with antibody levels with only 2 females having levels below the limit of quantification (LOQ) from days 35 or 57. Antibody development clearly affected the exposures achieved in both studies. However, given that antibodies did not develop in all animals, and some animals that developed antibodies had only a low titre and/or transient antibodies, adequate information on the toxicity corifollitropin alfa can still be gleaned from the studies.

Consistent with the pharmacology of corifollitropin alfa, changes in the gonads were observed at doses ≥1.64 mg/kg (exposure ratio based on AUC (ER_{AUC}) =1.6) in rats and ≥2.87 mg/kg (ER_{AUC}=6) in dogs. In female rats, changes were indicative of either ovarian stimulation (increase in mean ovary weight and increases in the incidences of animals with an increase in the number of follicles and corpora lutea) or non-stimulation/inhibition (increases in the incidence of animals with a decrease in the number of developing follicles, a decrease in the number of mature corpora lutea and an increase in interstitial cells). Non-stimulation/inhibition was observed in rats that had developed high titres of anti-corifollitropin alfa antibodies which, as well as neutralising corifollitropin alfa, presumably also affected endogenous FSH levels. Thus, the incidence of animals with ovarian stimulation was highest at the low dose (LD) and mid dose (MD), while the incidence of animals with ovarian non-stimulation/inhibition was highest at the HD, directly correlating with the incidence of animals with high titre antibodies. The presumed neutralisation of endogenous FSH in rats appears to have resulted in the pituitary increasing its secretion of FSH; hypertrophied cells with 'haloes' observed in the pituitary in some MD and HD rats were likely to have had increased secretion of FSH, and it was in these animals that increased ovarian interstitial cells were observed. These effects were not observed in the 13-week dog study, presumably because few dogs developed sustained high titre anti-corifollitropin alfa antibodies.

Other effects observed in the repeat-dose rat and dog studies appear to be mainly associated with hormonal changes. Serum progesterone was not measured in rats, but substantial increases were observed in female dogs at doses≥2.87 mg/kg (ER_{AUC}=6). Substantial increases in serum oestradiol were also observed in these animals. Oestradiol was not

detected in the serum from tested rats that had received 41 mg/kg, presumably due to antibody production having a neutralising effect.

Thus, changes in organs of the reproductive system (uterus, vagina, mammary glands, fallopian tubes and vulva) appeared to be associated with the well know stimulation of such organs by the sex hormones and for the most part have been observed previously with rFSH. For organs outside of the reproductive system, only minor histological changes (low incidence or of minor toxicological significance) were observed in rats. In dogs, changes in the adrenal glands (slight cortical cell atrophy and loss of normal architecture of the zona glomerulosa), skeletal muscle (eosinophilic inclusions), spleen (extramedullary haematopoiesis), bone marrow (changes in numbers of erythroid and myeloid elements and megakaryocytes), skin over mammary gland (increased amount of ground substance), and kidney and urinary bladder (urothelial hyperplasia), as well as reduced hair regrowth over shaved areas, were observed mainly in MD and HD females treated with doses that increased sex hormone levels. The findings in bone marrow and spleen correlate with the haematological changes (reduced haemoglobin and haematocrit levels with increases in reticulocytes) which are likely to be sex hormone-induced (Geil and Lamar, 1977), as are probably all of the other changes mentioned above. It is noted that, in addition to changes in organs of the reproductive system, adrenal changes, skin thickening, alopecia and urothelial hyperplasia, as well as increases in serum cholesterol and body weight, have all been reported in response to increases in sex hormone levels (Günzel *et al*., 1989; Johnson, 1989; Seibert and Günzel, 1994; Zayed *et* al., 1998; Maier and Herman, 2001). Effects of sex hormones on skeletal muscle have not been extensively studied, but Wiik (2008) has reported oestrogen receptors on human skeletal muscle. Some of the changes observed in dogs, most notably the haematological changes and long term effect on the mammary glands, reflect the unique sensitivity of this species to endocrine changes. It is generally accepted that these effects have limited relevance to humans (Seibert and Günzel, 1994; Maier and Herman, 2001).

Although the proposed indication relates only to females, all study results in males have been documented in this evaluation for completeness. In male rats and dogs, findings were largely restricted to the testes and epididymides (and seminal vesicles in rats) and are presumed to reflect stimulation of Sertoli cells where FSH receptors are located in males. The lack of findings in males in organs other than the reproductive organs supports the argument that the findings in females in organs other than those carrying the FSH receptor were due to the secondary effects of oestrogen and progesterone.

Recovery was investigated in both rats (3 weeks) and dogs (5 weeks), although interpretation was difficult as only control and HD groups were investigated. In rats all recovery animals at the HD developed high titre neutralising antibodies and in dogs there were only 2 recovery animals/sex/group. In rats, findings at the end of the recovery period (most notably, increased number of interstitial cells and reduction in number of developing follicles and in mature corpora lutea in the ovaries, and pituitary cells with 'haloes') mainly reflected ovarian inhibition as a result of high titre anti-corifollitropin alfa antibodies which were sustained during the recovery period.

In dogs, some of the changes observed at the end of treatment had reversed (most notably, some of the ovarian changes, some testicular changes, the skeletal muscles changes, bone marrow changes and adrenal cortical cell atrophy). However, many of the changes had not reversed or had only partially reversed by the end of the recovery period, and in the mammary gland there were new findings (lobular development and secretion). This may reflect the time required for sex hormone levels to steadily decline following the cessation of dosing; three weeks after the cessation of dosing, serum oestradiol concentrations were still

almost twice the basal level, while progesterone concentrations were ~30 fold basal levels. There is no reason to expect that the changes in dogs that appear to be associated with elevated sex hormone levels would not completely reverse after the sex hormone levels returned to base line.

Genotoxicity

Genotoxicity studies are generally not required for biotechnology-derived pharmaceuticals. These products would not be expected to interact with DNA or other chromosomal material, and the administration of large quantities of peptides/proteins in genotoxicity studies may yield uninterpretable results (International Conference on Harmonisation (ICH) Topic S 6). However, the potential genotoxicity of corifollitropin alfa was assessed in the standard battery of studies early in development (1996–1998). Corifollitropin alfa was not genotoxic in these studies.

Carcinogenicity

Carcinogenicity studies were not conducted. Standard carcinogenicity studies are generally considered to be inappropriate for biotechnology-derived pharmaceuticals, although product specific assessment of carcinogenic potential may still be needed (ICH Topic S 6). Since it is intended to give only single doses of corifollitropin alfa, although possibly over several cycles of treatment, the duration of dosing does not indicate a requirement for carcinogenicity testing. While some animals had hyperplasia of the uterine mesothelium in repeat-dose toxicity studies, it is not unusual for this type of product. As corifollitropin alfa is replacing a product with similar activity, the lack of carcinogenicity studies is acceptable.

Reproductive toxicity

Reproductive toxicity studies were adequate in terms of the types of studies conducted (time of dosing), dose levels, species and animal numbers. A considerable number of pilot studies were conducted in rabbits in order to select the most appropriate conditions for the main studies.

Rats

Male fertility studies

Although not relevant for the proposed indication, male fertility studies in rats were documented for completeness. There was no evidence of an effect of corifollitropin alfa on male fertility in either the pilot study (20 IU/kg SC every 2 days for 2 weeks prior to mating and during mating; n=8) or in the main study (5, 10 and 20 IU/kg SC every 2 days for up to 9 weeks prior to mating and during mating; n=20). Parameters investigated included mating rate, pregnancy rate, pre-coital interval, as well as litter parameters in the mated females. This is consistent with the lack of any gross or histological changes in the testes in the 13 week rat study at doses up to 200 IU/kg SC every 2 days.

Female fertility and embryofetal development studies

In the main study, which used only one dose level (20 IU/kg SC every 2 days), females were dosed from 1 week prior to mating up to gestation day (GD) 4. Fertility (mating and pregnancy) was not affected. The dose was superovulatory as revealed by 2-fold increases in corpora lutea number per dam and subsequent increased ovary weights. Although pre-implantation loss was increased, this was confounded by the higher number of corpora lutea so that the number of implantations/dam was actually higher in the test group compared with controls. Resorptions/dam and post-implantation loss were also increased, with numbers of live embryos/fetuses being slightly higher in the test compared with control group, and fetal

weights being lower. Broadly similar results were obtained in the pilot study using the same dose and have been observed with other gonadotrophins that induce superovulation. All these findings are what might be expected given the biological limit for the number of ova that can implant and grow in the uterus (Günzel *et al.*, 1989), but are not considered relevant to the clinical situation in which one or several fertilised ova are transferred to the patient's uterus. There was no evidence of teratogenicity in the main study in which drug was administered up to GD 4 (but given the 20 h half life in rats, exposure would have continued for some days after the last dose). Exposure ratio in this study was 0.6 based on AUC (assuming 7 doses).

Rabbits

Numerous reproductive toxicity studies were conducted in rabbits with toxicokinetic data in pregnant New Zealand White (NZW) rabbits collected in one study.

Table 2.

Dose (IU/kg)	Dose (mg/kg)	$AUC_{0-48\ h}$ (ng.h/mL)	C_{max} (ng/mL)	ER_{AUC}*	ER_{Cmax}
0.5	0.02	3.3	–	0.01	–
2	0.086	14	–	0.06	–
2.5	0.10	16	–	0.07	–
4	0.17	37	–	0.17	–
5	0.19	41	–	0.18	–
10	0.39	94	–	0.4	–
15	0.58	95	–	0.4	–
20	0.9	148	4.2	0.66	1
40	1.7	369	8.8	1.7	2
80	3.4	820	20	4	5
Human	150 mg	668^	4.35	–	–

^ $AUC_{0-\infty}$; * Exposure ratio (ER) calculated as animal $AUC_{0-48\ h}$ × 3/human $AUC_{0-\infty}$

Assuming comparable kinetics in pregnant and non-pregnant animals, with 3 doses per fortnight and linear kinetics with dose, the systemic exposure at other doses were estimated in the table above.

Fertility

There was no evidence of an effect on fertility (mating rate or pregnancy rate) in female rabbits given up to 40 IU/kg SC corifollitropin alfa on days -3 and -1 before mating provided that hCG was administered to ensure ovulation (and hence pregnancy).

Embryofetal development – litter parameters

A number of studies in the rabbit investigating the effects of corifollitropin alfa when administered prior to mating were designed to mimic the period of corifollitropin alfa exposure relative to conception and pregnancy in humans. Treatment in humans starts more than one week before ovulation. Treatment on Days -3 and -1 before mating in rabbits is probably a reasonable reflection of the human situation, although the rabbit ovulates after mating and does not have an oestrous cycle, so a comparison of length of treatment in relation to length of oestrous cycle cannot be made.

For an overview (bearing in mind the low animal numbers in pilot studies), results for ovary weight and litter parameters from all studies in which corifollitropin alfa was administered SC on Days -3 and -1 prior to mating are summarised in the following table (Table 3).

Table 3.

Dose (IU/kg)	Study no. PCD1415/SS096 (Pilot study) (n=6)				Study no. PCD2111/SU097 (main study) (n=20–32)			Study no. 1379/SS074 (Pilot study) (n=8)			Study no. PCD1227/SR135 (Pilot study) (n=5)	
	0	**0.5**	**2.5**	**5**	**0**	**2**	**4**	**5**	**10**	**15**	**20**	**40**
Ovary wt (g)	0.41	0.46	0.46	0.96	0.59	0.52	0.59	0.72	0.83	0.90	0.68	0.80
Corpora lutea/doe	8.3	11.2	17.7	nr	10.2	15.3	29.4	39.3	61.9	71.8	40.2	60.4
Implantations/doe	7.2	8.2	8.3	15.5	7.6	9.5	13.4	12.1	18.9	16.3	12.6	15.0
Pre-impl. loss (%)	13.4	25.0	45.2	nr	22.9	35.7	50.9	nr	nr	nr	nr	nr
Post-impl. loss (%)	9.3	1.9	33.7	36.0	10.0	24.5	36.0	9.5	64.8	68.0	55.1	69.0
Live fetuses/doe	6.5	8.0	6.2	10.2	7.5	8.0	9.4	5.9	10.6	6.4	5.8	5.2

nr not reported

Increases in mean number of corpora lutea/doe, although small, were observed at the lowest dose tested (0.5 IU/kg). From individual animal data it was apparent that some rabbits superovulated at 0.5 IU/kg, while most rabbits superovulated at 4 IU/kg, exposures well below the AUC at the MRHD.

At doses ≥5 IU/kg, there was a marked increase in the number of corpora lutea and a subsequent 2-fold increase in ovary weight. However, it is apparent from the results of the various rabbit studies that the true nature of the corpora lutea after administration of these doses cannot be accurately ascertained (and therefore, pre-implantation loss cannot be estimated, either). Pre-implantation loss was increased at 0.5–4 IU/kg, and although it could not be accurately determined at ≥5 IU/kg, presumably also increased at these doses. There were increases in the number of implantations/doe at all doses, which also appeared to reach a plateau at doses ≥5 IU/kg. Post-implantation loss was increased at doses≥2.5 IU/kg but there was no consistent difference in the number of live fetuses/doe, although results from the main study suggested small increases at the two doses tested (2 and 4 IU/kg), with reductions in fetal weights (findings similar to those seen in rats). In the main study, Humegon®, which contains FSH and LH, was used as a comparator. Results for Humegon® and corifollitropin alfa, each at 2 IU/kg, were comparable.

When corifollitropin alfa was administered during gestation (GD 0–4 or after GD 4), rather than prior to mating, no effects were observed on litter parameters at 20 IU/kg SC. At higher doses (≥40 IU/kg) there was no effect of treatment on pre-implantation loss or number of implantations, but there was an increase in post-implantation loss (mainly due to increases in late resorptions), with one doe suffering an abortion and a corresponding decrease in the number of live fetuses/doe. Taken together, it suggests the increase in apparent post-implantation loss may not only be a result of superovulation but also a result of hormonal changes. Given the increases in post-implantation loss observed in rabbits (and also observed in rats), it is appropriate that corifollitropin alfa should be contraindicated in pregnancy.

Embryofetal development – malformations

When corifollitropin alfa was administered to rabbits prior to mating (days -3 and -1), a dose-related increase in the incidence of fetal malformations was observed. Abnormalities included umbilical hernia, neural tube defects (exencephaly, anencephaly, hydrocephalus, and spina bifida), syringomelia, closed ventricular septum, and flexed forelimbs and hindlimbs. These occurred at doses ≥2.5 IU/kg. In the main study, Humegon®, at a dose of 2 IU/kg on days -3

and -1 before mating, caused a similar incidence of malformations as corifollitropin alfa at 4 IU/kg. Several fetuses from the Humegon® group had umbilical hernia, one of the more commonly observed malformations seen with corifollitropin alfa.

Data provided by the sponsor suggested the occurrence of malformed fetuses with corifollitropin alfa treatment were coincident with superovulation. A higher incidence of chromosomal abnormalities, including aneuploidy, has been observed in superovulated rabbits, and oocytes from other similarly-treated animals (Fujimoto *et al.*, 1974; Vogel & Spielmann, 1992). This is thought to occur during oogenesis primarily in the first meiotic division (Roberts *et al.*, 2005). The occurrence of malformations in the rabbit following treatment with corifollitropin alfa would be consistent with an increase in the incidence of chromosomal abnormalities. As the malformations were also observed with Humegon® when administered at equivalent time points, and have been reported for other gonadotrophins, these findings are not likely to be unique to corifollitropin alfa. Therefore, in clinical practice, provided ovarian stimulation is tightly controlled, there should be no greater risk of fetal abnormalities with corifollitropin alfa than with currently-registered FSH products.

A pre-postnatal reproductive toxicity study was not conducted and is not considered relevant for this type of drug.

Local tolerance

In a local tolerance study in rats investigating the SC, intravenous (IV) and intramuscular (IM) routes, injection site findings were similar in test and control groups for each route. The formulation tested in this study and many of the other non-clinical studies differed from that proposed for clinical use in that it lacked methionine (0.5 mg/mL). This omission is unlikely to affect the study results. Minor effects associated with the vehicle were observed after SC administration, and included interstitial haemorrhages and interstitial infiltration with inflammatory cells. Although corifollitropin alfa might not be expected to cause local irritation, it is noted that the concentration tested, 16.8 µg/mL, was considerably lower than the maximum concentration of corifollitropin alfa in the proposed clinical formulation (300 µg/mL). There was no evidence of a local irritant effect of corifollitropin alfa in the repeat-dose toxicity studies, although drug concentrations used were again low relative to the concentration of the proposed clinical formulation. Therefore local tolerance issues will need to be more fully addressed by clinical data.

Nonclinical Summary and Conclusions

An adequate package of nonclinical studies was submitted for a drug of this type, with all main studies being GLP compliant. Nonclinical studies were conducted with corifollitropin alfa produced by a different manufacturing process to that proposed for the clinical product. Bridging pharmacology and pharmacokinetic studies were conducted, and findings in toxicity studies would be expected to be similar for the clinical product.

Compared with rFSH, corifollitropin alfa had comparable binding affinity to the human FSH receptor, was weaker (about 1.5–2 fold) at producing a signal from the receptor, and had superior (about 2–4 fold) *in vivo* activity (augmentation of ovary weight and superovulation) presumably due to its longer *in vivo* half life. Superovulation in most rabbits was observed at a dose of 4 IU/kg on days -3 and -1 before mating (AUC at this dose was about one tenth that expected in patients at the recommended clinical dose).

Corifollitropin alfa showed high receptor specificity. At concentrations over >1000 times that at the maximum recommended human dose (MRHD), corifollitropin alfa showed no binding to, or bioactivity at, the LH receptor or in a Novascreen assay (41 receptors and

ion channels). It showed no bioactivity at the TSH receptor at a concentration of approximately 25 times that at the MRHD.

Cardiovascular safety issues are not predicted in clinical use as corifollitropin alfa did not affect hERG current in transfected HEK-293 cells at concentrations over >1000 times that at the MRHD and did not affect cardiovascular parameters in dogs administered a single SC dose giving an exposure (AUC) approximately 250 fold that at the MRHD.

The pharmacokinetics of corifollitropin alfa were characterised by slow absorption, relatively slow elimination (long half life), low volume of distribution (about the physiological volume of blood plus extracellular fluid) and dose linearity. Bioavailability of an SC dose was about 58% in humans, 40% in rats and 85% in dogs. In a distribution study in female rats, high concentrations of radioactivity were found in the ovaries (site of action), blood, injection site and kidneys (site of excretion). In urine, only intact corifollitropin alfa and its α and β subunits were detected. Excretion was largely (approximately 90%) via urine.

Corifollitropin alfa was pharmacologically active in mice, rats, dogs and rabbits. Single-dose toxicity studies using only one relatively low dose level (giving an AUC about 12–13 times that at the MRHD) were conducted in mice and rats. There were no deaths in rats, with findings considered to be related to the primary pharmacological activity of the drug. In mice, hepatotoxicity (hepatocellular necrosis) could not be ruled out as a drug-related effect.

Repeat-dose toxicity studies (13 weeks) were conducted in rats and dogs. A 39-week study was also conducted in male dogs. Despite neutralising antibody development hampering interpretation, particularly in rats, the studies still provided sufficient information on the toxicity of the drug. As expected, ovaries and testes were affected in both species. In female rats, changes in the ovaries were indicative of either ovarian stimulation or non-stimulation/
inhibition (the latter appeared to reflect antibody neutralisation of both drug and endogenous FSH). Other organs of the reproductive system (uterus, vagina, mammary glands) were affected in females of both species. Additionally, in female dogs, there were other changes, most notably in the adrenals, skin, skeletal muscle, plus reductions in red cell parameters, thrombocytopenia, and increases in cholesterol. All these changes appeared to be a secondary effect of increases in oestrogen and/or progesterone. Some of the changes are likely to be specific to the dog due to its known sensitivity to the sex hormones. The pituitary was affected in female rats, probably as a consequence of neutralisation of endogenous FSH by anti-corifollitropin antibodies. Many, but not all, of the changes observed were also seen in repeat-dose toxicity studies with rFSH. Findings were either reversible or expected to be reversible once hormone levels declined to baseline. Exposure ratios achieved in the repeat dose studies were adequate (for females, based on AUC, up to approximately 20 at the HD in dogs and up to 6 at the MD in rats [most HD rats developed neutralising antibodies]).

Genotoxicity studies, although not required for a biotechnology-derived drug, were conducted, with negative results. No carcinogenicity studies were conducted and this is acceptable.

Reproductive toxicity studies were performed in rats and rabbits. Under the experimental conditions tested, male and female fertility in rats was not affected, and fertility in female rabbits was not affected provided hCG was given to ensure ovulation. Broad trends

observed in both rats and rabbits following administration of corifollitropin alfa prior to mating were: superovulation (increase in ovary weight and number of corpora lutea/female), and increased pre-implantation loss, implantations/female and post-implantation loss, resulting in a small increase in live fetuses/female and small reductions in fetal weights. In rabbits given corifollitropin alfa on GD 0, 2 and 4, pre-implantation loss was not affected, but post-implantation loss was increased at doses ≥40 IU/kg (exposure ratio of 2 at 40 IU/kg). It is appropriate that corifollitropin alfa is contraindicated in pregnancy.

There was no teratogenicity observed in rats receiving corifollitropin alfa (20 IU/kg every 2 days) from 1 week prior to mating to GD 4 or in rabbits receiving corifollitropin alfa (20 IU/kg on GD 0–4). There was evidence, though, for a low incidence of malformations (including neural tube defects) in rabbits treated with corifollitropin alfa at ≥4 IU/kg (ER ~0.1) on days -3 and -1 before mating. Humegon® (FSH and LH), at a dose of 2 IU/kg on days -3 and -1 prior to mating, caused a similar incidence of malformations as corifollitropin alfa at 4 IU/kg. Some evidence was provided that the malformations induced by corifollitropin alfa occur only in rabbits that have superovulated.

The nonclinical data do not raise any issues of concern. Adequate studies for a drug of this type were submitted and revealed the expected pharmacological activity and a prolonged half life compared with rFSH. Repeated dose toxicity studies did not reveal any effects other than those considered to be related to the primary pharmacological activity of the drug or associated with secondary changes in sex hormones.

The sponsor proposes to contraindicate use of the product in pregnancy, which is appropriate given the embryofetal toxicity observed in rabbits. When administered prior to mating in rabbits, there was evidence for an increase in malformed fetuses. However, the same effect was observed for Humegon® and incidences were coincident with superovulation. Provided ovarian stimulation can be adequately controlled, there is unlikely to be a greater risk of abnormalities with this product compared with currently registered FSH-containing products. The sponsor's nonclinical expert noted that according to the Humegon® Periodic Safety Update Report (PSUR), Humegon® has not given rise to teratogenic effects in clinical use. This requires confirmation by the clinical evaluator.

IV. Clinical Findings

Introduction

The application is supported by a Phase II dose ranging study (38826) and two large Phase III randomised controlled trials comparing its efficacy with that of rFSH in terms of oocyte retrieval (107012) and the other with ongoing pregnancy as the primary endpoint (38819). The latter two studies are regarded as pivotal, and included a total of 1903 subjects, of whom 1023 received corifollitropin alfa. All of these studies were conducted using the protein free (pf) formulation as for marketing. Two earlier Phase II studies, 38805 and 38807 are included and are reviewed in the *Efficacy* section along with the other efficacy studies.

Studies 38801, 38802, 38823 and 38803 comprise an analysis of the pharmacokinetic (PK) and pharmacodynamic (PD) response to subcutaneously administered corifollitropin alfa together with PK measurements collected during the efficacy studies.

An ongoing safety/efficacy Study 38825 is also included. The data from this study, together with the safety data collected during the other studies in the application, and additional studies of pregnancy and neonatal follow-up, form the basis for the safety assessment of a total of 2185 subjects who have received corifollitropin alfa.

All of the reviewed studies have been conducted with appropriate ethical provisions and in accordance with good clinical practice. The statistical methodology employed is satisfactory.

Pharmacokinetics

Pharmacokinetic (PK) data is contained in most of the studies in the application, including not only those described in this section but also the efficacy and safety studies. Minor discrepancies between some of the values in these tables and those in the text descriptions are explained by the former being geometric mean±CV(%) and the latter usually arithmetic mean+standard deviation (SD). The coefficient of variation (CV) is frequently used as a readily interpretable indicator of the degree of inter-individual variation in pharmacokinetic and/or clinical response to the proposed treatment throughout this report.

In all of the described studies, pharmacokinetic measurements of corifollitropin alfa employed an enzyme-immunoassay, which was revalidated for measurement of the pf product when this was introduced. Samples were obtained (unless otherwise noted) in an intensive sampling protocol from baseline out to 336 hours (Day 15) following the injection of the product on Day 1. 4 mL blood samples were collected on Days 1 (just before injection and 2, 4, 6, 8, 12, 16 h after injection), 2 (24, 30, 36, 40 h), 3 (48, 54, 60 h), 4 (72 h), 5 (96 h), 6 (120 h), 7 (144 h), 9 (192), 11 (240 h), 13 (288 h) and 15 (336 h after injection).

Study 38801 was a phase 1, multicentre, repeated single-dose open-label trial of corifollitropin alfa carried out in male subjects with hypogonadotrophic hypogonadism (HH), and was the first human use of the substance. The trial was conducted by Organon between June 1997 and November 1998 and 13 subjects were recruited from four centres in Australia, Israel, Germany and the United Kingdom. Each was given four injections of 15 µg corifollitropin alfa (non-pf) subcutaneously at intervals of four weeks.

Serum concentrations of corifollitropin alfa were measured before each injection and at frequent intervals up to 336 h after the first and third injection; pharmacokinetic parameters calculated included maximal serum level of corifollitropin alfa (C_{max}), the time to attain maximal serum level (tmax), the area under the concentration versus time curve (AUC), the elimination half-life ($t_{½}$) and the clearance per kg of body weight (CL/kg).

Overall mean C_{max} was 0.43+0.12 ng/mL, achieved at a t_{max} of 46+18h, with a $t_{½}$ of 95+26h.

In this initial study of the use of corifollitropin alfa, blood samples for detection of antibodies to the substance were taken and no evidence of antibody formation was detected.

Study **38802** was a single centre study conducted between June-December 2000 by Dinox Medical Investigations in the Netherlands. Healthy female volunteers whose ovarian function was suppressed by an oral contraceptive preparation containing 50 µg ethinyloestradiol and 2.5 mg lynestrenol were given single subcutaneous injections of 15, 30, 60, or 120 µg corifollitropin alfa. The 31 subjects referred to actually represent 24 individuals as there were three groups of 8 subjects who received the 15, 30 and 60 µg doses and from these 24 a further group of 8 were selected for the 120 µg study (7 completed). The age range of the subjects was similar to that employed in other studies in the application, particularly pivotal trials 107012 and 38819, and the weight distribution of the subjects was similar to that of the heavier subjects of trial 38819 (see below).

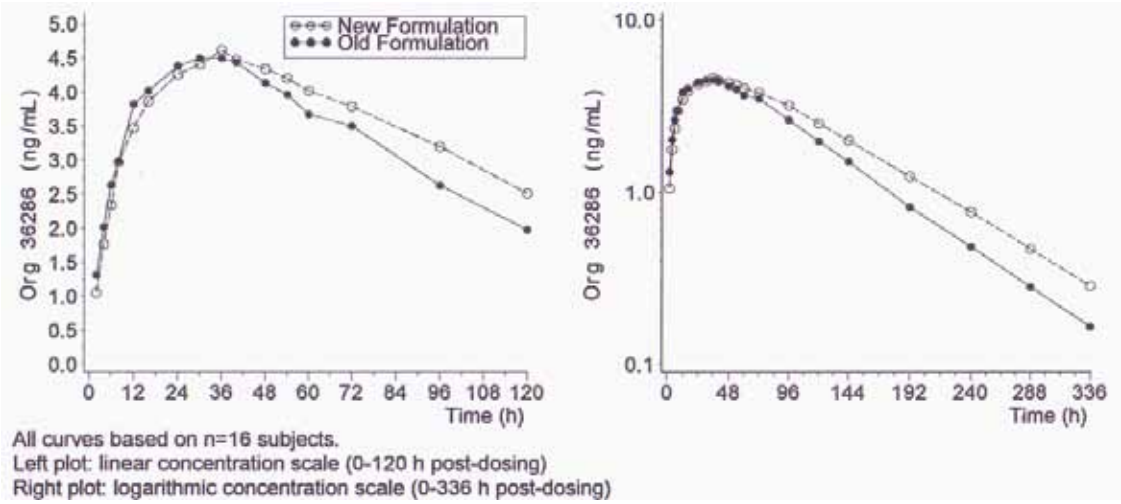
For estimation of ovarian follicular development, transvaginal ultrasonography was performed on Days –7, -1, 2-7, 9, 11, 13, 15, 17, 19 and 21. 5 mL blood samples for the assessment of LH, Inhibin-B and estradiol (E2) concentration in serum were collected at baseline, on Days 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 21 and on the day of post-treatment assessment. The results of these pharmacodynamic (PD) assessments are described above.

Values of C_{max}, t_{max} and $t_{1/2}$ were found similar to those in the pilot study. Coefficient of variation (CV) values for the various parameters ranging between 14 to 51% indicate significant between-individual variation in overall exposure and absorption and elimination times. Drug exposure per unit dose (dn-Cmax and dn-AUC) was consistent between the treatment groups, suggesting that absorption and elimination are dose independent across the range of dosages employed in the study.

Study **38823** was performed to investigate the effect of the formulation changes from the non-pf formulation to the pf formulation on the pharmacokinetics, pharmacodynamics and safety of corifollitropin alfa. This was another single centre study, performed between June and September 2002 under the sponsorship of Organon, again by Dinox Medical Investigations, using an open-label crossover design in 16 healthy female subjects whose pituitary function had been suppressed by the oral contraceptive preparation Marvelon (ethinyloestradiol 30 µg and desogestrel 150 µg). Each subject received 120 µg doses of each formulation in two treatment periods comprising three weeks observation with a four-week washout period in between.

T_{max} for the pf formulation was significantly longer at 40 h (range 24-96) by comparison with the original formulation (36 h, range 16-54). Likewise mean (CV %) half elimination time was longer at 71.5 (15.3) h by comparison with 62.6 (13.3) h. These differences are illustrated in the following figure (Figure 1):

Figure 1



Bioequivalence testing of exposure was performed by comparing the point estimates of the geometric means of C_{max} and AUC for the two formulations with their 90% confidence intervals (CI) as shown in the following table (Table 4):

Table 4

Parameter (unit)	Geometric Mean New (n=16)	Geometric Mean Old (n=16)	Point Estimate of true Ratio New/Old	90% Confidence Interval	Conclusion
C_{max} (ng/mL)	4.85	4.76	1.02	0.90-1.16	bioequivalent
$AUC_{0\text{-}tlast}$ (ng·h/mL)	667	569	1.17	1.10-1.25	not bioequivalent
$AUC_{0\text{-}\infty}$ (ng·h/mL)	701	586	1.20	1.12-1.28	not bioequivalent

Bioequivalent (Not bioequivalent): 90% CI inside (outside) acceptance range 0.80-1.25.

The formulations are shown not to be bioequivalent. The new (pf) formulation yields between 17 and 20% more exposure, attributable to the delayed kinetics of absorption and/or elimination as shown in Figure 1.

In view of these findings, the results of studies conducted with the non-pf formulation prior to April 2002 have been considered exploratory only for the purpose of this evaluation. These include Phase I clinical Trials 38801 and 38802 and Phase II clinical Trials 38805 and 38807.

A secondary objective of the study was the assessment of the PD response to the 120 µg dose using a protocol similar to that described for the previous study, with ultrasonographic measurement of follicular development along with measurement of inhibin-B as an index of follicular simulation and LH as evidence of suppression of endogenous ovarian function. In this study, ultrasonographic measurements were taken on Day -1, daily from Days 6 to 11, and then on Days 13 and 15 in each trial period. The results have been described above.

Study **38803** was conducted to assess the absolute bioavailability of the subcutaneous injection of the pf formulation, and was performed for the Organon division of Schering-Plough by FOCUS Clinical Development between April-November 2007. Using an open-label, crossover design 16 subjects were sequentially given corifollitropin alfa 100 µg by intravenous and subcutaneous injection in random order. Each administration was followed by a four-week observation period and a four-week washout period. The subjects were healthy females, mean age 24.3 years and mean body weight 64.5 kg, taking Marvelon for suppression of the pituitary/ovarian axis. The age (18-37 years) and body weight (55-79 kg) ranges are similar to those for subjects of the other studies in the application. All subjects were Caucasian.

Prior to the second treatment period, the possibility of antibody development was excluded by serological testing. There were no positive results. The antibody tests were repeated at the end of the second follow-up period, 4-5 weeks after the second drug administration, once again with negative results.

Of the 16 subjects, one (who had received the intravenous injection in the first sequence) was withdrawn for safety reasons on the criterion of a follicle size of $\geq$ 11 mm at baseline before the second injection (actual size > 17 mm). The all subjects pharmacokinetically evaluable (ASPE) group was therefore 15 subjects.

PD data in this study comprised transvaginal ultrasonography carried out for safety reasons, performed at baseline and on days 5-15 following each drug administration, and resulting in one exclusion as mentioned above. Serum LH was also measured as an indicator of suppression of ovarian function.

In addition to the standard intensive PK sampling as described above, more frequent sampling was undertaken within the first two hours following drug administration, so as to evaluate the time course of disappearance after the intravenous injection. Mean dose normalised C_{max} after subcutaneous injection was 0.036 ng/mL/µg administered, consistent with the values obtained in the other PK studies reviewed in this section. The key PK data for comparison of the two routes of administration and assessment of bioavailability are shown in the following table (Table 5):

Table 5

Parameters	Units	Treatment A (s.c.)		Treatment B (i.v.)	
		n	Mean (CV %)	n	Mean (CV %)
$t_{½}$	h	15	69.7 (8.68)	15	65.2 (7.64)
$AUC_{0\text{-tlast}}$	ng*h/mL	15	397 (22.6)	15	724 (18.8)
$AUC_{0\text{-}\infty}$	ng*h/mL	15	441 (19.8)	15	764 (18.1)

From these data the absolute bioavailability of corifollitropin alfa from subcutaneous injection was found to be 58%. The $t_{1/2}$ as shown in the above table following subcutaneous injection was statistically greater than that following intravenous injection. The difference is numerically small, however, would not be of biological significance and is probably attributable to overlap of the kinetics of the absorption and elimination processes.

The PK results from two Phase II feasibility studies of efficacy, **38805** and **38807** cannot be regarded as relevant to the present application in relation to the demonstrated degree of exposure, as both were conducted using the non-pf formulation. They nevertheless provide further confirmation that the pharmacokinetics of corifollitropin alfa is dose-proportional, at least within each study. In Study 38805, mean dn-C_{max} remains in the range 0.0222-0.0287 ng/mL/µg across the dose range 7.5-60 µg, and mean dn-AUC in the range 2.96-3.98 ng.h/mL/µg. In Study 38807, in which doses 120, 180 and 240 µg corifollitropin alfa were employed, the corresponding range of values for dn-C_{max} and dn-AUC were 0.0327-0.0357 ng/mL/µg and 4.07-4.44 ng.h/mL/µg respectively. The apparent difference in median value between the two studies is unexplained but may be attributable to uncontrolled demographic differences between the study populations.

In Study 38807, pharmacokinetic modelling was undertaken, examining the relationship between serum drug levels and demographic and biometric data. A significant positive relationship was detected between body weight and both clearance rate (CL) and volume of distribution (V). No significant variances were detected in relation to other factors examined, including age, dose level and ethnicity although assessment of the latter was probably not valid as most of the subjects were Caucasian. This factor was further examined in Study 107012 and it was found that bioavailability was 30% less in Asian subjects.

The remaining PK data relevant to the application were derived from the three major studies reviewed in the section on Efficacy; dose ranging Study **38826**, and the pivotal efficacy studies **107012** and **38819**. From these data, the following conclusions can be drawn:

1. T_{max} is consistent at between 41.6-43.8 h (combined value 44.1 h) and $t_{1/2}$ between 64.4-73.1 h (combined value 68.6 h). These are approximately 2-3 times the corresponding values

of 12 h and 40 h respectively quoted[1] for beta follitropin (recombinant FSH, Puregon®), the comparator product used in the efficacy studies of this application and a standard existing treatment in current use in Australia for the claimed indication. These characteristics are appropriate for the proposed duration of action of one week and justify the further clinical studies undertaken to test efficacy of the product used in this way.

2. Dose normalised drug exposure is consistent across Study 38819 and the dosage groups of Study 38826 with dn-C_{max} values between 0.0290-0.0293 ng/mL/µg and dn-AUC between 4.22-4.45 ng.h/mL/µg. Exposure was higher in Study 107012 with corresponding values of 0.0360 and 5.91 respectively for these parameters. This has been attributed to the lower body weight of the subjects in that study.

3. Between-individual variation in drug exposure is high with CV values consistently over 30% at various levels of dosage. CV of the combined PK data, with the omission of that from Study 38819 in which there were no absorption phase data, was 37% for dn-C_{max} and 31% for dn-AUC. Assessing the clinical significance of these figures is difficult as there are no PK data collected under the same trial conditions for the comparator product rFSH. The closest comparison available to this evaluator is PK data reviewed for TGA on the subcutaneous administration of a recombinant LH to a demographically similar population of female subjects. For C_{max}, CV values varied from 11-24% (mean 17%). For AUC, the mean CV value was 25% with values at 5/7 dose levels being 25% or below.

An uncertain proportion of this high level of variance in exposure can be attributed to variation in body weight and to Asian ethnicity as already described, and could therefore be anticipated and avoided by appropriate dose adjustment, as indeed recommended in the proposed Product Information (PI) in relation to body weight. Otherwise, excessive variance in exposure with this product is a matter of concern as under exposure would lead to impaired therapeutic response and overexposure would have safety implications, as the major adverse event reported -ovarian hyperstimulation syndrome (OHSS) - is clearly dose-related.

No explanation is presented for the apparent dependence of dose normalised drug exposure (and therefore dose requirement) on body weight. Clearance data indicate that the product is distributed into the extracellular space. Variations in body weight amongst adults of similar stature are likely to be due to variations in fat cell mass, with extracellular space being relatively constant. It should be noted that the drug exposure/body weight relationship was originally noted in Study 38807, in which the non-pf formulation was used. The relationship may in fact be less robust for the pf formulation, although a clinically significant relationship with body weight is supported by the finding of similar total exposure in subjects with body weight $\leq$ 60 kg after treatment with 100 µg doses in Study 107012 by comparison with subjects with body weight > 60 kg who received 150 µg doses in Study 38819.

Drug Interactions

Drug interaction studies have not been performed and are not seen to be relevant as the product would be unlikely to compete in drug clearance mechanisms. No studies have been performed in patients with impaired renal or hepatic function but it is unlikely that patients with such conditions would be undertaking the treatment programs in which the product is used.

[1] Current Australian product information, MIMS database, August 2009

Pharmacodynamics

The expected biological response to the administration of FSH is a rise in the germinal epithelium derived peptide inhibin-B in either males or females, and in females an associated rise in oestradiol. In males, minimal if any rise in the sex steroids testosterone and oestradiol is expected, nor in females a rise in progesterone, these steroid hormones being responsive in normal reproductive physiology to luteinising hormone (LH). Measurements of these hormones have been carried out in most of the studies in the application and are presented as evidence of an appropriate pharmacodynamic response to the administration of corifollitropin alfa.

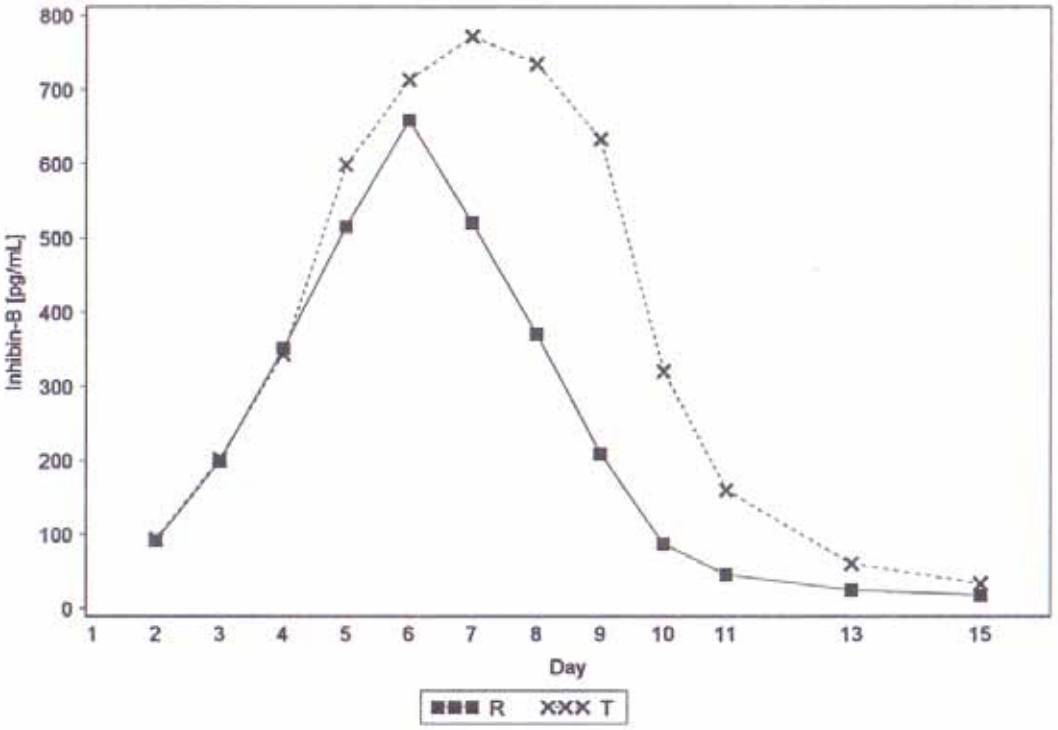
In the preliminary Study **38801**, a rise in inhibin-B, but no significant change in testosterone or oestradiol, was observed. In these hypogonadal male patients, inhibin-B was as expected very low at baseline and rose to a peak of approximately 150 pg/mL at (on average) Day 6, falling back to baseline by the time of the next injection after 28 days but remaining still well above baseline at 14 days. Similar responses were observed after both the first and third injections.

In Study **38802**, corifollitropin alfa was first given to human females and the pharmacodynamic (PD) response was observed by measurement of the number and size of ovarian follicles developing and measurement of serum levels of LH, inhibin-B and oestradiol. The primary PD parameter was the maximum number of follicles observed on ultrasound in each patient on any given day. The median value of maximum numbers observed were 1, 1, 15 and 27 in the 15, 30, 60 and 120 µg dosage groups, respectively. Higher size classes (8-10 and 10-12 mm) of follicles were only observed in the 60 and 120 µg dosage groups and follicles >12 mm diameter only observed in 120 µg dosage group. No follicle >16 mm diameter was observed in this study.

Biochemical evidence of induction of follicular growth was consistent with these morphological findings. At baseline, the majority of subjects showed inhibin-B levels below the lower limit of quantification (LLOQ); two days after drug administration, these levels had increased to a mean of 146 and 203 pg/mL in the 60 and 120 µg dosage groups respectively and to means of 295 and 990 pg/mL respectively after 5 days, whereas no significant increases occurred in the lower dosage groups. Following Day 6, the levels of inhibin-B declined. No significant rises of oestradiol occurred at any stage.

PD evidence of ovarian response was also obtained in Study **38823,** in which 120 µg doses of the old (non-pf) and new (pf, as proposed for marketing) formulations were given. The median (range) number of follicles > 5 mm observed on the day of maximum response (n_{max}) was 10 (7-15) for the pf formulation by comparison with 8 (7-11) for the non-pf. Follicles in the 12-14 mm range were observed in the majority of the subjects, and in the 14-16 mm range in about half. Follicles >16 mm in diameter were observed in 2 subjects after the pf and in 4 after the non-pf formulations. These statistics are descriptive only, and the difference between the formulations would not be clinically significant, but the findings demonstrate a response to the treatment in the same range as that shown in Study 38802. This was further confirmed by the demonstration of a rise in serum inhibin-B which was more sustained in the new (pf) formulation group, as shown in the following figure (Figure 2):

Figure 2 Serum Inhibin-B levels.



With the pf formulation, the inhibin-B response is maintained for approximately 10 days. The study was not designed for the difference between the groups to be analysed statistically, but the pattern is consistent with the observed difference in pharmacokinetic parameters and suggests that the proposed for marketing formulation is more appropriate for its planned therapeutic role in sustained stimulation of follicular development.

Measurements of serum LH were generally below LLOQ as expected. Six subjects showed measurable levels at some point of the study, presumably reflecting either lack of compliance with or partial lack of efficacy of the oral contraceptive formulation. The finding does not affect the results of the study.

Efficacy

Study **38805** was a Phase II trial undertaken to assess the feasibility of inducing monofollicular ovulation using a single injection of corifollitropin alfa. It was carried out under the sponsorship of Organon between August 2001 and October 2002 at five centres in Belgium, the Netherlands and the United Kingdom (UK). Using a double-blind placebo-controlled design, 55 female subjects with World Health Organization (WHO) Group 2 anovulatory infertility were randomised to receive 7.5, 15, 30 or 60 µg corifollitropin alfa (non-pf), or placebo.

As the dosage regimen, formulation used, and therapeutic indication all differ from the specifications of this application, this trial has not been evaluated in detail from an efficacy standpoint. In brief summary, the product did not prove to be effective, in the doses employed, for the intended therapeutic outcome. The PK data have been reviewed above in regard to demonstration of dose proportionality, and the subjects are included in the safety population.

Standard controlled ovarian stimulation protocol - applies to all studies

All of the remaining clinical studies in this section employ a similar protocol to enable the assessment of a single injection of corifollitropin alfa, designed to be effective for seven days,

as the initiating treatment in a "short protocol" controlled ovarian stimulation regimen. The results for subjects using this active treatment are compared with a control group receiving the standard established treatment which is a daily injection of rFSH on each of these seven days. "Short protocol" COS refers to a regimen which is started at the beginning of a natural menstrual cycle with FSH given for approximately 10 days to induce follicular growth, a GnRH agonist (following down-regulation), or alternatively antagonist, given to prevent premature endogenous LH surge and ovulation, and then human chorionic gonadotropin (hCG) given to trigger ovulation once there is evidence of follicular maturity. All of the studies in this application employed the GnRH antagonist ganirelix (Orgalutran®), 0.25 mg daily, for endogenous LH suppression.

Following feasibility trial 38807, in which the day of starting GnRH antagonist treatment was flexible and determined by the observation of a ≥ follicle mm in diameter on ultrasonography, it was decided to fix the GnRH antagonist start day to stimulation Day 5 for all of the subsequent trials.

In all of the studies, the comparison of corifollitropin alfa with the daily 150 IU (200 IU in Study 38819) rFSH reference treatment occupied the first seven days of each treatment cycle only. From Day 8 onwards, subjects in both active and control groups continued to receive usually 150 units, but in some cases up to 200 units, of rFSH daily until follicular maturation was sufficient for the administration of hCG to trigger ovulation, but not beyond a maximum duration of stimulation treatment of 19 days. The day of hCG administration was established by the criterion of at least three follicles ≥17 mm being observed on ultrasonography. hCG (10,000 IU Pregnyl®) was then given along with the daily dose of rFSH and ganirelix. About 30-36 hours later, oocyte retrieval was undertaken followed by *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) and embryo transfer 2-5 days later. No more than three embryos were to be transferred. Luteal phase support with progesterone was left to be determined by the investigator's usual practice.

In the overall efficacy data set, approximately half of the subjects (46-54% in the various treatment groups) defined "male factor" as the reason for infertility, and therefore probably had no significant abnormality of endocrine or other reproductive physiology themselves. The remainder had a variety of causes of subfertility typically seen in patients attending IVF clinics, which were almost exclusively the source of recruitment of subjects. Overall, the study population is quite representative of the target therapeutic group for this product and therefore appropriate for evaluation.

Study **38807** was carried out between July 2001 and October 2002 under the sponsorship of Organon at 3 centres in the Netherlands and Belgium. This was a phase II feasibility, dose ranging trial to assess the dose of corifollitropin alfa required to initiate follicular development in patients undergoing COS in an IVF/ICSI program.

The data from the study is not formally evaluable for this application, as the non-pf formulation was used, but its findings informed the design of subsequent studies and are accordingly presented.

The study was divided into two phases. Phase 1 was an exploratory study involving six subjects. The first two of these were given a 120 µg dose of corifollitropin alfa. In each, follicular development did not progress after Day 7. The remaining four patients were given 180 µg doses. Oocytes were retrieved in the range 10-21 per patient with 7-14 embryos being obtained. One of the four patients had an ongoing singleton pregnancy. As a result of Phase 1, the planned dosages for Phase 2 were revised from a 60-120 µg range to a 120-240 µg range.

Following these exploratory studies, Phase 2 was commenced using an open-label randomised design in which single doses of 120, 180 and 240 µg corifollitropin alfa (referred to as Org 36286 in tables) were given to parallel groups each of 25 subjects. A fourth active control group received 150 µg rFSH daily. Recruited subjects were females of couples with an indication for COS and IVF or IVF/ICSI aged ≥18 and ≤39 years at the time of screening, with normal menstrual cycle length (24-35 days), and body mass index (BMI) ≥18 and ≤29 kg/m2.

Each study subject was treated for one COS cycle using the standard protocol described above. A total of 99 subject were randomised, 25 to each of the active treatment groups and 24 to the control group. The intention to treat (ITT) population comprised all of these except for one patient in the 180 µg dosage group. The per protocol population (total of 87 subjects) were evenly distributed between the treatment groups. Baseline demographics were evenly distributed between the treatment groups except that the 120 µg treatment group was on average some 2 years younger and 2 kg lighter in body weight. Most of the patients were Caucasian.

The primary efficacy parameter was the total dose of rFSH required, from Day 8 of the cycle onwards, to achieve the criteria for hCG administration. The results are shown in the following table (Table 6):

Table 6

	Treatment group			
	120 µg Org 36286	180 µg Org 36286	240 µg Org 36286	Puregon®
Total dose (IU) of Puregon®	(N=25)	(N=23)	(N=23)	(N=23)
Median (Min-Max)	450.0 (0.0-1050.0)	450.0 (150.0-900.0)	450.0 (150.0-1200.0)	300.0 (150.0-900.0)

Secondary efficacy parameters in the study included the frequency of cycle cancellation, the numbers of cumulus-oocyte complexes recovered, and the numbers of resulting embryos and pregnancies. The results for oocyte retrieval are displayed in the following table (Table 7):

Table 7

Number of cumulus-oocyte complexes recovered	Treatment group			
	120 µg Org 36286	180 µg Org 36286	240 µg Org 36286	Puregon®
per attempt	(N=25)	(N=24)	(N=25)	(N=24)
Mean (SD)	11.0 (7.1)	11.1 (7.5)	12.0 (7.3)	7.9 (4.1)
Median (Min-Max)	11.0 (0.0-28.0)	10.0 (0.0-32.0)	11.0 (0.0-25.0)	8.0 (0.0-16.0)
per stage*	(N=23)	(N=22)	(N=23)	(N=23)
Mean (SD)	12.0 (6.5)	12.1 (6.9)	13.0 (6.6)	8.3 (3.8)
Median (Min-Max)	11.0 (3.0-28.0)	11.0 (2.0-32.0)	12.0 (1.0-25.0)	8.0 (3.0-16.0)

*Restricted to subjects with oocyte retrieval.

Note that in the "per attempt" results, oocytes are not counted in the small number of subjects (maximum 1-2 per group) who did not undergo oocyte retrieval, so that there are some zero results. The "per stage" results are a more accurate reflection of the process of follicular simulation. Equivalent numbers of oocytes were developed in each of the treatment groups, with no dose effect discernible, and with the response in each case being greater than that demonstrated for the control FSH treatment.

Of the 98 subjects treated (ITT population), 30 achieved pregnancy on biochemical grounds. Of these, 2 had an ectopic pregnancy and 3 miscarried. Of the remaining 25 ongoing

pregnancies, a multiple pregnancy occurred in 1 subject in the 180 µg group, 2 in the 240 µg group, and 1 in the active control group.

Statistical analysis of the PK data from this study provided evidence of a relationship between body weight and drug exposure, as discussed above.

Biochemical monitoring included measurement of inhibin-B during the phase of follicular simulation. A rise occurred in all treatment groups and was unexpectedly greatest in the lowest dose (120 µg) group. No explanation is given for the finding, but it might be related to the lower body weight of the subjects in this dosage group as described above.

Study **38826** was an open-label Phase II dose-finding trial conducted between May 2003 and May 2004 in 17 European IVF centres (one UK) under the coordination of Organon. Subjects received a single injection of varying doses of corifollitropin alfa to initiate multifollicular growth, again for the first seven days of a COS in patients undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and using the protocol described above. A total of 325 subjects were randomised and 315 treated, 77 with a 60 µg dose, 77 with 120 µg and 79 with 180 µg. A control group of 82 subjects were treated with 150 IU of rFSH daily. The mean (SD) age was 32.1 (3.7) years and the majority of subjects (95.2%) were Caucasian. Inclusion criteria were the same as those for Study 38807. The dose range of corifollitropin alfa used reflects the finding of the previous dose ranging Study 38807 in which a dose response relationship was not established, and it appeared that a maximal effect may have been occurring with all doses used.

In this, and the other remaining studies evaluated in this section, the active treatment used was the pf formulation of corifollitropin alfa as proposed for marketing in this application. The reference treatment, rFSH, was given in the form of Puregon®. This product is marketed in Australia and is frequently used as the FSH preparation for COS. The formulation used appears to be the same or similar to that marketed in Australia although it is noted that in Study 38807, a methionine free preparation was used. The current Australian formulation contains methionine and benzyl alcohol[2]. The difference may reflect the time elapsed since the study was performed.

The primary efficacy parameter for the study was the number of cumulus-oocyte complexes retrieved. The results are illustrated in the following table which also includes the data on numbers of embryos and ongoing pregnancies, which were secondary efficacy parameters (Table 8):

[2]Current Australian product information, MIMS database, August 2009

Table 8

		60 µg Org 36286 (N=78)	120 µg Org 36286 (N=77)	180 µg Org 36286 (N=79)	150 IU recFSH (N=81)
Number of cumulus-oocyte-complexes recovered					
per started cycle	N	78	77	79	81
	Mean (SD)	5.2 (5.5)	10.3 (6.3)	12.5 (8.0)	7.7 (6.3)
	Median (Min-Max)	4.5 (0-28)	10.0 (0-30)	12.0 (0-46)	7.0 (0-39)
per stage *	N	50	72	74	73
	Mean (SD)	8.1 (4.9)	11.0 (5.9)	13.4 (7.6)	8.6 (6.1)
	Median (Min-Max)	7.0 (2-28)	10.0 (2-30)	12.5 (2-46)	7.0 (1-39)
Number of good quality embryos obtained [a)]					
per started cycle	N	78	77	79	81
	Mean (SD)	1.4 (1.9)	3.2 (2.7)	3.3 (3.4)	2.2 (2.3)
	Median (Min-Max)	0.5 (0-8)	3.0 (0-12)	2.0 (0-16)	1.0 (0-9)
per stage **	N	49	72	74	73
	Mean (SD)	2.2 (2.0)	3.5 (2.7)	3.5 (3.4)	2.4 (2.3)
	Median (Min-Max)	2.0 (0-8)	3.0 (0-12)	2.0 (0-16)	2.0 (0-9)
Number of ongoing pregnancies					
per started cycle	N	78	77	79	81
	n (%)	12 (15.4%)	12 (15.6%)	11 (13.9%)	11 (13.6%)
per stage ***	N	44	70	70	66
	n (%)	12 (27.3%)	12 (17.1%)	11 (15.7%)	11 (16.7%)

* Restricted to subjects with oocyte retrieval.
** Restricted to subjects with IVF/ICSI.
*** Restricted to subjects with embryo transfer.
[a)] Embryo quality was assessed on day of embryo transfer.

This table shows how the efficacy of the treatment must be assessed in relation to the processes of the IVF/ICSI protocols as well as by direct measurement of the numbers of oocytes retrieved. Whether on a per-started cycle or per-stage basis, as already described above, there is a clear dose relationship from 60 to 180 µg in terms of oocyte retrieval, which proved to be statistically significant ($p<0.0001$). As well as the number of follicles recovered, the size distribution of follicles also varied with the dose of corifollitropin alfa given. On Day 8, the mean numbers of follicles≥ 11 mm in diameter were 6.8, 10.1 and 12.8 with the increasing doses of corifollitropin alfa and 7.8 in the active control group. On the day the administration of hCG the number of follicles≥ 17 mm were 3.7, 4.2, 4.6 in the three corifollitropin alfa dosage groups and 4.0 in the active control Puregon® group.

A larger number (34) of subjects in the 60 µg dosage group did not proceed to embryo transfer, by comparison with 5 in each of the higher dosage groups. The main reason given was inadequate ovarian response. However, of those who did proceed, a higher proportion (27.3% versus 17.1% and 15.7%) achieved ongoing pregnancy, so that the absolute numbers of patients achieving ongoing pregnancy were similar (11 or 12) in all of the corifollitropin alfa dosage groups as well as the active control group. The majority (80.4%) of the ongoing pregnancies were singletons.

There was a relationship between corifollitropin alfa dosage and the duration and amount of rFSH given from Day 8 onwards. The median duration of treatment from Day 8 up to hCG was 4, 3 and 2 days for the 60 µg, 120 µg and 180 µg Org 36286 groups, respectively, and 2 days for the Puregon® group. The median total amount of rFSH administered was 600 IU, 450 IU and 300 IU for the 60 µg, 120 µg and 180 µg corifollitropin alfa groups, and 1350 IU for the Puregon® group.

During the first five days of stimulation, serum E2 and inhibin-B levels increased more rapidly in all corifollitropin alfa dosage groups than in the Puregon® group. Between Days 6-8, these levels declined rapidly in the 60 µg group, reached a plateau in the 120 µg group and increased further in the 180 µg Org 36286 group. On the basis of these data it would be reasonable to conclude that the optimal dose of corifollitropin alfa in this patient group was more likely between 60 and 120 µg than between 120 and 180 µg.

Study **107012** was a Phase III, multicentre randomised, double-blind, active-controlled trial of a single injection of 100 µg corifollitropin alfa using the common COS protocol as described for Study 38826, and undertaken between December 2006 and November 2007. The subjects were again women with normal menstrual cycles undergoing COS for IVF/ICSI but in this case weighing 60 kg or less, and were recruited from 2 Asian and 7 continental European sites. 44% of the subjects were Asian. 396 eligible women were randomized and treated; 268 subjects in the corifollitropin alfa group and 128 subjects in the rFSH group.

Exclusion criteria applying to both this study and the other major efficacy trial 38819 were described.

The trial was designed and powered as an equivalence study of the active treatment by comparison with the reference therapy which was again 150 IU of rFSH daily, with the primary endpoint for determination of equivalence being the number of oocytes retrieved in each group. The predefined margins for demonstration of equivalence, for the difference in mean numbers of oocytes between the test and control groups, were (-3, +5). The investigators' rationale for the lower margin was that if the test treatment resulted in 3 or more oocytes less than the reference treatment, such difference was considered as clinically relevant because 3 oocytes usually result in one good quality embryo for transfer or freezing. With regard to the upper margin, assuming the treatment target to be the induction of an average of 12-13 oocytes in both test and reference groups, an excess of more than 5 oocytes would be undesirable as subjects with more than 18 oocytes are known to have an increased risk of Ovarian Hyperstimulation Syndrome (OHSS).

The SD for numbers of retrieved oocytes at the dose levels of corifollitropin alfa which produce these target levels of ovulation, and in the reference group, are in the range 6-8 (see Table 8). Although there are no comparisons of the test treatment against placebo in the submitted data, all of the trials being active-controlled, it can be anticipated on the basis of the variance stated that the specified margin for equivalence of -3, +5 would be less than half of the variance about the mean comprising the 95% CI of the absolute treatment effect, and therefore of acceptably small size[3].

In summary, the specified equivalence margins are based on sound clinical reasoning and appear statistically valid. Using these margins, the population sample size was based on calculations to demonstrate equivalence with 90% power.

The results for the primary and principal secondary efficacy parameters (ITT population) are shown in the following table in a similar format to that showed for Study 38826 (Table 9):

[3] Non-inferiority trials: determining whether alternative treatments are good enough. Scott I A. Med J Aust 190:326-330 (2009).

Table 9

		100 µg Org 36286 (N=268)	150 IU recFSH (N=128)
Number of cumulus-oocyte-complexes recovered			
per started cycle	N	268	128
	Mean (SD)	13.3 (7.3)	10.6 (5.9)
	Median (Min-Max)	12.0 (0-46)	10.0 (0-33)
per stage *	N	266	127
	Mean (SD)	13.4 (7.3)	10.7 (5.9)
	Median (Min-Max)	12.0 (0-46)	10.0 (0-33)
Number of good quality embryos obtained at Day 3 [a]			
per started cycle	N	263	127
	Mean (SD)	3.4 (3.0)	2.9 (3.0)
	Median (Min-Max)	3.0 (0-15)	2.0 (0-15)
per stage **	N	259	123
	Mean (SD)	3.4 (3.0)	3.0 (3.0)
	Median (Min-Max)	3.0 (0-15)	2.0 (0-15)
Number of ongoing pregnancies			
per started cycle	N	268	128
	n (%)	68 (25.4%)	44 (34.4%)
per stage ***	N	246	121
	n (%)	68 (27.6%)	44 (36.4%)

* Restricted to subjects with oocyte retrieval.

** Restricted to subjects with IVF/ICSI.

*** Restricted to subjects with embryo transfer.

a Excluding subjects who had embryos transferred or cryopreserved before Day 3. For subjects with missing values, zeros were imputed if no embryos were transferred or frozen at all. Otherwise missing values remained missing.

As can be seen from the upper panels, the numbers of oocytes recovered was of similar magnitude in the treatment and control groups and slightly greater in numbers for the corifollitropin alfa group, in which the mean (SD) number of cumulus-oocyte-complexes retrieved per started cycle in the ITT group was 13.3 (7.3) by comparison with 10.6 (5.9) for the 150 IU rFSH group. The estimated treatment difference, adjusted for age group (< 32, ≥ 32 years), planned fertilization procedure and center, was 2.5 cumulus-oocyte-complexes in favor of the Org 36286, group, with a 95% confidence interval of 1.2, 3.9. This is well within the predefined equivalence range of (-3, +5) complexes and indicates that the two treatment groups are equivalent. The difference between the numbers of recovered complexes in the corifollitropin alfa and control rFSH groups was also statistically significant ($p<0.001$), but the sponsors do not claim superiority as the trial was not designed on that basis.

The median duration of FSH stimulation was 9 days for both groups. The total dose of additional rFSH administered after Day 7 was also similar, 300 IU for corifollitropin alfa and 275 IU for the rFSH group. Hormonal measurements showed that inhibin-B and oestradiol initially rose more rapidly following corifollitropin alfa but tended to remain stable (inhibin particularly) after Day 5 in the corifollitropin alfa group while continuing to rise in the FSH group. It is difficult to make any clinical correlations with these differing patterns of change.

It will be noted from Table 9 that the numbers of embryos obtained were greater in the corifollitropin alfa group but the ongoing pregnancy rate was less (25% versus 34% per started cycle, 28% versus 36% per stage). These differences were found not to be statistically significant, but only by a narrow margin ($p= 0.06$). The cancellation rate (no embryo transfer) was 8.2% for corifollitropin alfa and 5.5% for rFSH; the difference was not significant ($p= 0.41$).

The overall pattern of pregnancy related clinical outcomes is displayed in the following table (Table 10):

Table 10

		100 µg Org 36286 N=268	150 IU recFSH N=128
		N n (%)	N n (%)
Biochemical pregnancy	Per attempt	268 101 (37.7)	128 58 (45.3)
	Per embryo transfer	246 101 (41.1)	121 58 (47.9)
Clinical pregnancy	Per attempt	268 78 (29.1)	128 48 (37.5)
	Per embryo transfer	246 78 (31.7)	121 48 (39.7)
Vital pregnancy	Per attempt	268 69 (25.7)	128 45 (35.2)
	Per embryo transfer	246 69 (28.0)	121 45 (37.2)
Ongoing pregnancy	Per attempt	268 68 (25.4)	128 44 (34.4)
	Per embryo transfer	246 68 (27.6)	121 44 (36.4)
Singleton	Per ongoing pregnancy	68 49 (72.1)	44 34 (77.3)
Twins	Per ongoing pregnancy	68 19 (27.9)	44 10 (22.7)
Miscarriage	Per clinical pregnancy	78 10 (12.8)	48 4 (8.3)
	Per vital pregnancy	69 1 (1.4)	45 1 (2.2)
Ectopic pregnancy	Per embryo transfer	246 8 (3.3)	121 4 (3.3)
	Per biochemical pregnancy	101 8 (7.9)	58 4 (6.9)

n = number of subjects with data; N = the total number of subjects.

Apart from the vital pregnancy rate being less, the miscarriage rate was higher in the corifollitropin alfa group. Had these differences in pregnancy rates and other outcomes proved to be statistically significant, it would have been difficult to attribute this to any specific factor. Apart from the oocyte retrieval rates being equivalent or better for the corifollitropin alfa group, the numbers and quality ratings of embryos transferred were closely similar between the two groups. The implantation rate was slightly less than the corifollitropin alfa group, 23.4% compared with 28.5% for rFSH.

In summary, this study yields a robust finding of efficacy for the applicant product being equivalent to comparator for its intended purpose of stimulation of ovulation. The data on final clinical outcome (successful pregnancy) leave some uncertainty but are insufficient for analysis/evaluation.

Study **38819** was undertaken, to the understanding of this evaluator, in response to an FDA requirement that pregnancy be used as the primary endpoint and in conjunction with the previous Study 107012 is pivotal to the application. The trial was conducted between June 2006 and January 2008 in 34 international centres; 13 in the USA, 1 in Canada, 3 in the UK and 17 in continental Europe and was designed as a randomised, double-blind active controlled non-inferiority study with 1400 subjects to be recruited in a 1:1 active:control ratio. The study employed a similar protocol to that of Study 107012 to examine the efficacy of a single corifollitropin alfa injection, this time given to women weighing >60 kg and ≤90kg, using a dose of 150 µg as informed by the PK studies reported above. A higher dose of gonadotrophin (200 IU rFSH) was also used as comparator treatment in the control group.

The primary efficacy measure was ongoing pregnancy assessed at least 10 weeks after embryo transfer; oocyte retrieval was included as a co-primary endpoint. A total of 1509 subjects was randomized, of whom 86% were Caucasian. For the difference between the ongoing pregnancy rates of the test and control treatment groups a predefined limit of -8% was set for the lower bound of the two-sided 95% confidence interval (CI). The quantum of

this non-inferiority margin is arbitrary: in justifying it, the application states (summary of clinical efficacy) that *"this limit of -8% is considered a clinically acceptable difference between the treatment groups. Although an 8% difference would be relevant for an individual subject seeking to become pregnant after IVF*

treatment it should be considered in the context of existing differences in routine pregnancy rates between centers, countries and regions". The statement is supported by references to pregnancy rates in various regions. The scientific validity of the margin is difficult to assess but it appears reasonable to this evaluator, although if anything somewhat generous. The occurrence of pregnancy, being measured by event rate rather than as a variable with mean and standard deviation, cannot be characterised by variance limits within individual data sets and therefore the accepted method of assessing the non-inferiority margin by comparison with the confidence interval of the treatment effect[4] cannot be readily applied. One relevant observation from the submitted data is that an 8.8% difference (27.6% versus 36.4%) was observed in the ongoing pregnancy rate per embryo transfer in Study 107012, as shown above in Table 10, which appears attributable to random factors other than the efficacy of the ovulation stimulation treatment itself.

In addition to this specified non-inferiority margin, pre-defined margins of -3, +5 were established, as in Study 107012, for the lower bound of the 95% CI for the difference between the treatment groups in numbers of retrieved oocytes (co-primary endpoint), on the basis of equivalence testing.

In the trial, 757 subjects were randomised to receive corifollitropin alfa and 752 subjects to rFSH. One of the corifollitropin alfa and two of the rFSH subjects received the wrong treatment allocation. The results for both primary endpoints, together with the figures on embryo transfer, are summarised in the following table (Table 11):

Table 11

[4] Scott I A. (2009). Non-inferiority trials: determining whether alternative treatments are good enough. *Med J Aust* 190:326-330.

		150 µg Org 36286 (N=756)	200 IU recFSH (N=750)
Number of cumulus-oocyte-complexes recovered			
per started cycle	N	756	750
	Mean (SD)	13.7 (8.2)	12.5 (6.7)
	Median (Min-Max)	13.0 (0-65)	12.0 (0-39)
per stage *	N	732	742
	Mean (SD)	14.1 (7.9)	12.7 (6.7)
	Median (Min-Max)	13.0 (0-65)	12.0 (0-39)
Number of good quality embryos obtained at Day 3 [a]			
per started cycle	N	743	741
	Mean (SD)	4.5 (4.3)	4.4 (3.9)
	Median (Min-Max)	4.0 (0-34)	4.0 (0-29)
per stage **	N	714	728
	Mean (SD)	4.6 (4.3)	4.4 (3.9)
	Median (Min-Max)	4.0 (0-34)	4.0 (0-29)
Number of ongoing pregnancies			
per started cycle	N	756	750
	n (%)	294 (38.9%)	286 (38.1%)
per stage ***	N	672	704
	n (%)	294 (43.8%)	286 (40.6%)

* Restricted to subjects with oocyte retrieval.
** Restricted to subjects with IVF/ICSI.
*** Restricted to subjects with embryo transfer.
a Excluding subjects who had embryos transferred or cryopreserved before Day 3. For subjects with missing values, zeros were imputed if no embryos were transferred or frozen at all. Otherwise missing values remained missing.

The mean ongoing pregnancy rates (lower panels) and numbers of cumulus-oocyte-complexes retrieved per started cycle are closely similar for the test and reference treatments and meet the respective non-inferiority and equivalence margins for these two parameters as defined above. The two-sided 95% CI for the treatment difference on pregnancy rates was -3.9, 5.7, readily excluding the predefined non-inferiority margin of -8%; with reference to the comments above about the selection of the non-inferiority margin, it can be observed *post hoc* that a more conservative margin could readily have been satisfied. Additionally, the estimated difference of 1.2 cumulus-oocyte complexes per started cycle in favour of the corifollitropin alfa treatment was statistically significant (p=0.001). For the ongoing pregnancy rates, the estimated treatment difference between the two groups remained comparable when adjusted for age group (< 32 years, ≥ 32 years) and region (Europe, North America). Whether it is appropriate to set non-inferiority and equivalence margins for separate parameters in the same study could be debated, but the observed data speak for themselves and there appears little doubt to this evaluator that equivalence could have been demonstrated for the pregnancy as well as the ovulation parameters, had it been pre-specified.

Study **38825**, an uncontrolled, multicentre, open-label trial of the use of corifollitropin alfa in the common COS protocol described above, was initiated in September 2006 and was still ongoing at the cut-off date for this application of 25 April 2008. The principal aim of the study was the collection of data on safety and immunogenicity, which are discussed in the Safety section of this evaluation report, but some limited efficacy data are also available.

Subjects qualifying on essentially the same inclusion and exclusion criteria applying to the pivotal efficacy studies were recruited from 30 centres in Australia (5 centres), Argentina (6 centres), Brazil (2 centres), Chile (2 centres) and 8 EU countries (total 15 centres). Treatment with corifollitropin alfa 150 µg was planned for 3 cycles and efficacy data was collected in the first cycle. By the cut-off date, 681 subjects had been treated for at least one cycle.

Subjects were on average aged 32.9 years and weighed 67.0 kg (BMI 24.2). 93.8% were Caucasian. The median duration of extra rFSH simulation prior to hCG administration was 2 days and the median dose of rFSH administered from Day 8 onwards was 400 IU, the maximum allowable daily dose of the protocol having been increased from 200 to 225 IU. The average number of cumulus-oocyte complexes per attempt was 11.9 (SD 7.2), with a biochemical pregnancy rate of 31.1% per attempt. These data are closely similar to those obtained in the corifollitropin alfa treatment groups of the pivotal efficacy studies.

Study **38833** was an uncontrolled, single centre feasibility trial of corifollitropin alfa conducted earlier in the development program (December 2005-July 2007). A long GnRH agonist protocol was used with the aim of preventing premature LH surges. Two groups each of 25 patients received 100 µg and 150 µg of corifollitropin alfa, resulting in a mean number of oocytes of 15.4 and 17.8 respectively. Corresponding ongoing pregnancy rates were 24.0% and 33.3% respectively. Further data from this trial is presented in the section on safety below.

Subpopulations

The influence on response to the test treatment of demographic and other physical attributes of the subjects was examined in some of the included trials. In Study 38826, a negative correlation was established, most significantly at the 60 µg dose level, between clinical responsiveness, as assessed by oocyte retrieval, and body weight and body mass index (BMI). This correlates with the pharmacokinetic data from the study, which indicated decreased exposure in subjects of greater body weight.

Rate of oocyte retrieval was also observed to be negatively influenced by increasing age, increasing baseline FSH, and decreasing basal antral follicle count, all indicators of diminishing ovarian reserve.

Ethnicity of the subjects is a difficult factor to assess, as it is closely correlated with the geographical region in which particular trials were done, which will in turn influence covariables such as the body weight of subjects, other demographic variables, and subtle variances in clinical practice. Despite the reduced bioavailability reported in Study 107712, the mean number of oocytes retrieved in Asian centres in that trial was higher (14.9) compared to Europe (12.0).

Apart from the influence of body weight, which is allowed for in the dosing recommendations (see PI, Attachment 1), the influence of these factors is not clinically significant. The various factors referred to above which contribute to diminished ovarian responsiveness will simply lead to an increase in failure rate and/or need for upward titration of gonadotrophin dose, all of which are outcomes which would be expected by clinicians working in the field, and which had equal influence in both the corifollitropin alfa and reference treatment groups.

Conclusion on efficacy

The trial data submitted by the sponsor clearly show their product to be effective as an initial form of FSH stimulation during the first week of COS, by comparison with the chosen reference treatment of 150 units of rFSH daily (200 units daily in Study 38819). Its suitability for the claimed indication is therefore crucially dependent on whether the reference treatment represents the accepted standard therapeutic approach. Standard protocols[5] employ

[5] *In vitro* fertilisation (review), R Paulson. UpToDate reference program version 17.2, updated June 12 2009.

doses which may be above 150 units daily, in the range 150-225 units. Current available prescribing information[6] also specifies daily doses of 150 units upwards, up to 300 units or more in resistant cases. The fixed daily dose of 150 units also removes from the clinician the capacity for early phase dose adjustment, although the clinical trial protocols did allow adjustment of dosage from Day 5 onwards.

In this context, particular note is taken of the following statement in the sponsor's clinical overview; *"The lower number of oocytes retrieved in this latter group* (referring to the reference group) *may be explained by the protocolized regimen not allowing the dose to be increased during stimulation if the starting dose of 150 IU rFSH appeared to be too low for a specific subject"*. The converse of this argument, of course, is that had the protocol allowed for individual adjustment of dosage, greater numbers of oocytes may have been retrieved in the reference group.

Particular note should nevertheless be taken of the outcome of trial 38819 in which the reference treatment dose was higher (200 IU), but there was very close correspondence between the clinical outcomes of the test and reference groups.

Considering all these factors, it is the finding of this evaluation that the reference treatment chosen is a valid comparison. Any minor difference in efficacy of the fixed dose regimen is in any case buffered by the capacity of the managing clinician to adjust gonadotrophin dosage in the remaining 2-4 day period between the 7-day action period of corifollitropin alfa and the day of hCG administration.

Safety

This section will address four separate safety issues and observed or potential adverse effects of the applicant product, as follows:

1. Effects associated with an excessive degree of the physiological action of FSH, particularly OHSS.

2. Hypersensitivity to the product, given its structure and therefore antigenic potential.

3. Follow-up of pregnancy and neonatal outcome after use of the product.

4. Monitoring of any observed hypothetically potential effects of the product unrelated to its intended physiological/pharmacological action.

In each of the clinical studies reviewed in earlier sections of this report, the occurrence of adverse events (AE) and serious adverse events (SAE) was closely monitored along with measurement of routine haematological and biochemical laboratory parameters and vital physical signs, local tolerance of the product (injection site reactions) and measurement of anti-corifollitropin alfa antibodies.

The data from these safety evaluations was summarised with clarity and in considerable detail in the sponsor's Summary of Clinical Safety. In the application, data from 12 completed clinical trials are included and are reviewed in the Summary of Clinical Safety, as follows:

[6] Current Australian product information, MIMS database, August 2009. Current USA drug information, follitropin beta (recombinant FSH).

- four Phase I trials (studies 38801, 38802, 38803 and 38823);

- four Phase II trials (studies 38805, 38807, and 38826 and 38833);

- two active-controlled Phase III trials (studies 107012 and 38819);

All of the above studies have already been described in the sections on pharmacodynamics, pharmacokinetics and efficacy. Additionally, two pregnancy and neonatal follow-up trials are included (studies 38817 and 38827). Study 38817 addresses the safety issues, including neonatal follow-up, of ongoing pregnancies established during Trials 38805 and 38807. Study 38827 deals with the same issues in follow-up of Study 38826.

Interim safety data from ongoing trials are also included in the Summary of Clinical Safety, derived from the following studies:

- one Phase II trial (Study 107010); this is an ongoing study, outside the stated indication, in which small doses (15 to 30 µg) of corifollitropin alfa are given in an attempt to induce monofollicular ovulation. It has not otherwise been evaluated in this report.

- one uncontrolled Phase III multicycle trial (Study 38825)

- four pregnancy and neonatal follow-up trials (studies 38834, 38821, 107014, and 38829). These latter four studies report pregnancy, as well as neonatal follow-up of ongoing pregnancies established during studies 38833, 38819, 107012, and 38825, respectively.

For Study 107010 the cut-off date for the interim safety analyses was 12 February 2008. For the remaining trials the cut-off date was 25 April 2008.

Exposure to the drug

In the included clinical trials comprising the corifollitropin alfa development program, a total of 2185 subjects have received at least one dose of the product. Of these, 309 received single doses of 100 µg, mostly in Study 107012. The majority, 1107 subjects, have received 150 µg doses, mostly in the pivotal efficacy Study 38819 and the ongoing open-label Study 38825. Of these 1107, 681 received one dose, 321 two doses, and 105 were given three doses.

Adverse event reporting

AE and SAE were documented in all studies but are best evaluated in the pivotal efficacy/safety trials 107012 and 38819, which contained the majority of the subjects given doses of 100 µg or above (mostly 150 µg). Furthermore, in these studies it is possible to compare AE occurrence rates with those reported in the control groups receiving FSH. The results of event reporting in these two trials is illustrated in the following table (Table 12):

Table 12

Event type	107012				38819			
	100 µg Org 36286 (N=268)		150 IU recFSH (N=129)		150 µg Org 36286 (N=755)		200 IU recFSH (N=751)	
	n	%	n	%	n	%	n	%
Subjects with AEs	148	55.2	69	53.5	481	63.7	459	61.1
Deaths [a)]	0	0.0	0	0.0	0	0.0	0	0.0
Subjects with SAEs	20	7.5	8	6.2	34	4.5	28	3.7
Subjects who discontinued due to AEs (according to EoT-form)	0	0.0	0	0.0	16	2.1	3	0.4
Subjects with drug-related AEs [b)]	56	20.9	32	24.8	177	23.4	187	24.9
Subjects with AEs of known severe intensity	8	3.0	6	4.7	55	7.3	43	5.7

[a)] Irrespective of time point of death.
[b)] Relationship specified as 'Definite', 'Probable', 'Possible', according to the investigator.

Both AE and SAE were reported more frequently in Study 38819, in which higher doses of both test and reference products were used. None of the event categories in the above table show any difference between test and reference groups in either study, with the exception of a larger number of subjects discontinuing due to AEs in the corifollitropin alfa group of Study 38819 (16 versus 3 control subjects). Whether the AEs in this group were non-specific or felt to be drug-related was not specified in the study report and could not be identified by the clinical evaluator

In ongoing trial 38825, AE reporting rate was similar to the above incidence but diminished with increasing number of cycles of treatment. AE reporting rate was 44.3%, 31.5% and 22.3% and SAE 3.2%, 1.6% and 0% in cycles 1, 2 and 3 respectively.

The qualitative pattern of adverse event reporting showed no difference between the test and reference groups. Pelvic pain and/or discomfort were reported by 10-15% of subjects in efficacy studies employing 100-150 µg corifollitropin alfa or 150-200 IU rFSH. Incidence of symptoms suggestive of OHSS occurred for either group in the range 5-8%, as discussed in more detail below. A variety of non-specific AEs, for example, headache, gastrointestinal complaints, respiratory symptoms, were reported by subjects in both test and reference groups and were mostly classified as non-treatment related by the investigators.

Deaths

No deaths have occurred in any of the reported studies, including the ongoing trials.

Ovarian hyperstimulation syndrome (OHSS)

A potential hazard of this long acting, standard dose, FSH preparation is that there might be an increased risk of OHSS because the option does not exist for the clinician to adjust the starting dose of FSH based on a previous history of hyperresponse, or other perceived risk factors for OHSS. Incidence of some degree of OHSS, while undesired and unintended, is inevitable in COS treatment programs[7], one of the challenges of which is keeping such side-effects to a minimum while at the same time minimising the incidence of failed cycles which are distressing to the patient who then requires repeat treatment which would otherwise not

[7] *In vitro* fertilisation (review), R Paulson. UpToDate reference program version 17.2, updated June 12 2009.

have been needed. The question for this evaluation therefore is not whether OHSS occurred, but whether its incidence and severity were equivalent to or less than that of the reference rFSH treatment. This question is most easily answered if the test and reference treatments have closely equivalent measures of efficacy; this is the case for Study 38819 (see PK section) but not for the other major Study 107012 in which, although it was not a planned outcome, efficacy as measured by oocyte retrieval was significantly greater for the test treatment (see PK section).

Symptoms of some degree of OHSS occurred in all the included studies, but for the reasons given in the previous paragraph are best evaluated in controlled trials 107012 and 38819, in which incidence and severity can be compared with control observations. The relevant results from these studies are shown in the following table which shows the incidence of symptoms in the upper panel and the grade of symptoms in the lower panel (Table 13).

Table 13

	107012				38819			
	100 µg Org 36286 (N=268)		150 IU recFSH (N=129)		150 µg Org 36286 (N=755)		200 IU recFSH (N=751)	
	n	%	n	%	n	%	n	%
OHSS (AE)	18	6.7	6	4.7	53	7.0	47	6.3
OHSS (SAE)	7	2.6	0	0.0	14	1.9	9	1.2
Discontinuation due to OHSS (AE)	0	0.0	0	0.0	12	1.6	1	0.1
Discontinuation due to OHSS (SAE)	0	0.0	0	0.0	4	0.5	0	0.0

OHSS grade	107012				38819			
	100 µg Org 36286 (N=268)		150 IU recFSH (N=129)		150 µg Org 36286 (N=755)		200 IU recFSH (N=751)	
	n	%	n	%	n	%	n	%
Grade I (mild)	9	3.4	4	3.1	22	2.9	27	3.6
Grade II (moderate)	5	1.9	1	0.8	17	2.3	10	1.3
Grade III (severe)	4	1.5	1	0.8	14	1.9	10	1.3
Total	18	6.7	6	4.7	53	7.0	47	6.3

If a subject had more than one OHSS event, the highest grade is taken into account.

While analysis of this data is qualitative only, it appears that both incidence and severity of OHSS was greater by comparison with control in the corifollitropin alfa subjects of Study 107012, who also experienced higher rates of oocyte retrieval, whereas the OHSS experience of subjects in both test and reference groups of Study 38819 was very similar, corresponding with their likewise similar levels of oocyte retrieval. This four-way analysis, while fortuitous, strongly suggests that the incidence of OHSS is more strongly associated with the intensity of FSH receptor dependent ovarian stimulation achieved, rather than that of the specific drug used.

The safety data relating to OHSS risk is flawed to some extent by the exclusion from the trials of patients with known risk factors for this complication. These include a past history of ovarian hyper-response or of OHSS itself, a history of polycystic ovary syndrome (PCOS) or a basal antral follicle count of >20. In the trial setting, these exclusions were of course prudent but the fact that they were made indicates that the sponsor recognises that the non-titratable dose inherent in the nature of corifollitropin alfa means that such patients are at greater risk. The proposed PI specifies these conditions as a contraindication to its use.

Hypersensitivity

Corifollitropin alfa is a foreign protein, despite having close structural homology with the human hormones FSH and chorionic gonadotrophin, and therefore potentially immunogenic. Potential signs and symptoms of hypersensitivity were assessed by local tolerance scoring and vital sign measurements 30 minutes after each injection, by review of AE reporting, and by measurement of anti-corifollitropin alfa antibodies and anti-CHO protein antibodies on pre-and post-treatment blood samples. CHO (carbohydrate) proteins, or glycoproteins, are the class of hormones to which gonadotrophins, including FSH and hCG, belong.

Blood samples were obtained and screened with the anti-corifollitropin alfa assay from the majority (97.4%) of subjects treated in the Phase I studies, 92.6% of Phase II subjects, and from 1681 (98.7%) of the subjects in the completed and ongoing phase III trials 38819, 107012 and 38825. The majority of the Phase I and II subjects were also tested with the anti-CHO protein assay, and no positive results were obtained in either this, or the anti-corifollitropin alfa assay.

Of the 1681 tested Phase III subjects, 2 from Study 38819 and 1 in the second cycle of Study 38825 showed low levels of binding on the anti-corifollitropin alfa assay. In each case the titre was too low to allow specific identification of antibodies. In these samples, the binding activity could be neutralised by addition of either corifollitropin alfa or FSH. Neither showed activity in a FSH bioassay. All three of the subjects had a normal ovarian response to corifollitropin alfa, two became pregnant, and none reported any AE suggestive of allergy or anaphylaxis. Subsequent blood samples (taken 6-12 months later) from all three subjects showed negative results in the binding assay.

These serological abnormalities are of equivocal analytical significance, non-specific, did not persist, and occurred only in a very small number of subjects. The author of the sponsor's safety summary considers the findings not clinically relevant, and this evaluator agrees with that assessment.

Local tolerance was best assessed in the controlled trials 38819 and 107012. There were no reports of moderate or severe redness, itching, swelling or pain when assessed 30 minutes after injection. Mild reactions, mainly redness, were reported by 7.7% of corifollitropin alfa subjects, 6.6% of rFSH subjects, and by 7.5% and 6.7% following the respective corresponding placebo injections. These results are obviously non-specific.

Overall, there has been an adequate assessment of the possibility of hypersensitivity reaction with no evidence of this being found.

Follow-up of pregnancy and neonatal outcome

With this new NCE being used immediately prior to pregnancy, close monitoring for adverse effects on mothers, foetuses and born children is essential although the nature of the product does not give rise to any specific expectation of the possibility of adverse pregnancy or neonatal effects.

Studies 38817 and 38827 provide follow-up of these issues from the early clinical trials 38805/38807 and 38826 respectively. The pooled data from these two studies shows an apparent excess of adverse event reports from subjects in the corifollitropin alfa groups. Of these 51 subjects, 35 (68.6%) reported AE and 8 (15.7%) SAE, by comparison with 10 (47.6%) and 2 (9.5%) in the control rFSH groups. There was also an excess of SAE in liveborn infants from the corifollitropin alfa subjects, 12 infants (21.1%) experiencing a total of 18 SAE compared with 3 in three infants (13.0%) from control subjects. A breakdown of these events by system and organ class appears in the following table (Table 14):

Table 14

System Organ Class	Preferred Term	placebo (N=1)		Org 36286 (N=57)		recFSH (N=23)	
		n	%	n	%	n	%
Metabolism and nutrition disorders	TOTAL	0	0.0	5	8.8	1	4.3
	Hypercalcaemia	0	0.0	1	1.8	0	0.0
	Hypernatraemia	0	0.0	1	1.8	0	0.0
	Hypoglycaemia	0	0.0	2	3.5	1	4.3
	Underweight	0	0.0	2	3.5	0	0.0
Respiratory, thoracic and mediastinal disorders	TOTAL	0	0.0	3	5.3	1	4.3
	Acute respiratory distress syndrome	0	0.0	0	0.0	1	4.3
	Immature respiratory system	0	0.0	1	1.8	0	0.0
	Neonatal aspiration	0	0.0	1	1.8	0	0.0
	Pneumothorax	0	0.0	1	1.8	0	0.0
Hepatobiliary disorders	TOTAL	0	0.0	1	1.8	0	0.0
	Hyperbilirubinaemia neonatal	0	0.0	1	1.8	0	0.0
Musculoskeletal and connective tissue disorders	TOTAL	0	0.0	0	0.0	1	4.3
	Foot deformity	0	0.0	0	0.0	1	4.3
Pregnancy, puerperium and perinatal conditions	TOTAL	0	0.0	5	8.8	0	0.0
	Premature baby	0	0.0	5	8.8	0	0.0
Congenital, familial and genetic disorders	TOTAL	0	0.0	3	5.3	0	0.0
	Cerebral palsy	0	0.0	1	1.8	0	0.0
	Congenital brain damage	0	0.0	2	3.5	0	0.0
	Syndactyly	0	0.0	1	1.8	0	0.0
General disorders and administration site conditions	TOTAL	0	0.0	1	1.8	0	0.0
	Oedema	0	0.0	1	1.8	0	0.0

Based on MedDRA version 10.1.
A subject can have adverse events in more than one class/term.

For a number of reasons it is difficult to evaluate these data, or to draw an adverse conclusion regarding the apparently greater number of events in the corifollitropin alfa group. The numbers of subjects are small, and the proportion of test versus reference subjects varies between studies. The dose range is different from that in the pivotal studies, up to 180-240 µg (non-pf) in one of the originating studies (38807). Most importantly, all of the studies contributing to the follow-up trials 38817 and 38827 were of open-label design, so that both subject and investigator would be aware who had received "new" as opposed to conventional treatment, which could cause considerable bias.

Further information on pregnancy/neonatal outcome is available from follow-up of subjects who participated in the large randomised controlled trials which contribute the bulk of the efficacy and safety data in the application. Examination of the pooled data from studies 38834, 38821, 107014, and 38829, which provides this follow-up along with that of ongoing open-label Study 38825, shows a different picture. Adverse event reporting by system and organ class during pregnancy and puerperium in the mothers from these studies shows no trend towards difference between test and reference groups. The numbers of foetuses resulting from these pregnancies with at least one AE in the follow-up period likewise shows no excess for the corifollitropin alfa group, as shown in the following table (Table 15):

Table 15

System Organ Class	Preferred Term	Org 36286 (N=738)		recFSH (N=410)	
		n	%	n	%
Respiratory, thoracic and mediastinal disorders	TOTAL	16	2.2	16	3.9
	Neonatal respiratory distress syndrome	9	1.2	6	1.5
Pregnancy, puerperium and perinatal conditions	TOTAL	47	6.4	34	8.3
	Jaundice neonatal	5	0.7	7	1.7
	Premature baby	40	5.4	22	5.4
	Small for dates baby	3	0.4	5	1.2
Congenital, familial and genetic disorders	TOTAL	35	4.7	23	5.6
	Patent ductus arteriosus	5	0.7	5	1.2
NOT CODED	TOTAL	14	1.9	8	2.0
	NOT CODED	14	1.9	8	2.0

Based on MedDRA version 10.1.
A subject can have adverse events in more than one class/term.
NOT CODED means that the reported term was not yet coded at the time of the interim analysis.

Note that the number of live births followed up is substantial (total 1148), and there is no trend towards either group. While these data represent only an interim analysis, and follow-up monitoring should continue, the data are reassuring regarding absence of any pregnancy or neonatal adverse effect attributable to the corifollitropin alfa treatment.

Data on congenital malformations observed at the foetal stage of development are sourced from trials 38817 and 38827, a data set which is not ideal for reasons outlined above. The data includes foetuses assessed *in utero* by ultrasound and also the outcome of pregnancies that were medically terminated or in which intrauterine death had occurred. Of 62 foetuses in the corifollitropin alfa group, 9.7% had minor and 4.8% major malformations. The corresponding figures from 24 foetuses from rFSH treated mothers were 16.7% and 4.2%, so that within the limits of the data there is no suggestion of an increased incidence associated with the test product. Equivalent data from later trials has yet to be compiled.

Possible effects other than ovarian stimulation

A molecular analogue of the type comprising this NCE has the hypothetical potential to bind to and activate receptors, particularly glycoprotein receptors, in other tissues resulting in physiological or non-physiological effects other than the intended biological response of ovarian follicular stimulation resulting from interaction with the FSH receptor. The likelihood of such receptor-interaction related adverse effects extending to areas outside the domain of known glycoprotein hormone actions is, however, diminished by the structural composition of the analogue molecule. It exclusively uses component sequences from the native human species hormones FSH and hCG, without any of the artificial amino acid sequence substitutions used in other therapeutic analogues of hormones, for example those of insulin and somatostatin. As such it is relatively unlikely to act as a ligand in other biological systems. Nonclinical data in the application showed that corifollitropin alfa at a concentration up to and including 5000 ng/mL did not show any binding to a range of receptors and ion channels in cardiovascular and renal assay panels, and in animal studies it did not exhibit any acute effects on the functionality of pivotal organ systems, including the cardiovascular, respiratory, renal, and central nervous systems.

Safety monitoring in the included studies revealed no clinically significant or unexpected changes in haematological or biochemical parameters, vital signs or physical findings. Some minor variations in blood cell count were observed, particularly an upward shift in the leucocyte count, but this was not different between the test and reference treatment groups and may represent a paraphenomenon of ovarian hyperstimulation.

Summary on safety

In any controlled ovarian stimulation regimen, higher doses or longer duration of FSH therapy will give rise to higher rates of ovulation, improved pregnancy rates, a greater

probability of multiple pregnancy, and correspondingly a greater incidence of OHSS-related adverse events. A number of varieties of COS protocols have evolved over time in an attempt to achieve a satisfactory balance of benefit versus risk in this equation. The use of corifollitropin alfa in the proposed protocol is, so far as ovarian stimulation is concerned, simply another variation on this theme and there is nothing in the safety data in the application to suggest a qualitatively novel or specific pattern of adverse event attributable to the product.

It is nevertheless clear that the "one size fits all" approach of the weekly injection - notwithstanding the dose adjustment based on body weight - does remove from the prescribing clinician some capacity for empirical dose adjustment and thereby diminish the probability of avoiding adverse events - particularly OHSS and related conditions - predictable on the basis of risk factors such as PCOS and other conditions mentioned in the discussion on *Safety* above. This hazard has been appropriately addressed by the sponsor in the prescribing advice contained in the Precautions and Contraindications sections of the draft PI, although the recommendation for exclusion of such patients from using the treatment should in the opinion of this evaluator be more definite (see discussion below).

There appear to be no safety concerns related to pregnancy, childbirth and neonatal/infant health consequent on the use of corifollitropin alfa. The relatively high morbidity and foetal mortality evident in the data are known features of assisted reproductive technology programs and/or the populations which present for them, and on the basis of the submitted data appear unrelated to whether corifollitropin alfa or the standard treatment rFSH is used for stimulation of follicular development.

No other or unexpected safety issues have been identified in the trial data.

Post marketing experience

Not yet relevant or available.

Clinical Summary and Conclusions

Corifollitropin alfa in the formulations presented in this application is shown by the submitted data to be an effective analogue of FSH for inducing ovarian follicular development in COS programs. It is also shown to be acceptably safe, assuming that standard postmarketing safety monitoring will be continued. If approved, this product will add to the range of FSH protocols already in use for the stated indication. In a previous TGA evaluation (already referred to in this report), the following statement is noted, and supported by this evaluator: *"the approach of titrating dosage according to response is familiar to clinicians with experience in this area and necessary because of the large individual variation in responsiveness to gonadotrophins, whatever the indication for ovulation induction. The abundance of published studies using different dosages suggests that ideal ovulation induction regimens are yet to be established for most indications."*

The applicant product presents a convenient and less invasive method of administering FSH for controlled ovarian stimulation. In the overall context of this complex form of treatment, the impact on convenience of the weekly versus daily injection is arguable. There is a trade-off in the form of less capacity for dosage adjustment and an increased risk of excessive stimulation particularly for some patient groups who are therefore excluded. The usefulness of the product in the therapeutic armamentarium for COS regimens will doubtless be determined by experienced clinicians who are the only ones who use such substances for this indication. Under these circumstances, there would seem no objection to registration. The hypothetical possibility of adverse reactions other than those related to hyperstimulation, due to unexpected receptor interaction or other effects of this NCE, has been reasonably evaluated

by the sponsor but cannot be absolutely excluded and must be the subject of ongoing safety monitoring. Given that cautionary note, **it is recommended that the application be approved**.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan with their submission which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The Risk Management Plan proposed the following in regard to identified safety concerns:

- Routine pharmacovigilance activities: Evaluation and expedited reporting of Individual Case Safety Reports; Preparation of labelling tables; Preparation of periodic reports; Literature screening and surveys; Signal detection activities.
- The following Additional Pharmacovigilance activities:
  - Standardised questionnaire for each case of Ovarian Hyperstimulation Syndrome (OHSS) to collect all relevant data as complete and effective as possible.
  - Completion of repeated exposure immunogenicity Trial 38825 will inform the probability of any clinically relevant anti- corifollitropin alfa antibodies or drug-related hypersensitivity in the target population.
  - Completion of the ongoing pregnancy and neonatal follow-up trials to quantify whether there is an increased risk versus reference treatment and to monitor the incidence and nature of congenital malformations after corifollitropin alfa treatment.
- An assessment by the sponsor of the requirement to provide a Risk Minimisation Plan concluded that:
  - Routine risk minimisation activities were sufficient.
  - No routine or additional risk minimisation activities were needed for hypersensitivity, since the available data did not suggest a specific safety concern in terms of a hypersensitivity reaction or anti-corifollitropin alfa antibody formation.
- Proposed risk minimisation activities:
  - Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for the important identified risk OHSS and the other safety concerns, multiple pregnancy, spontaneous abortion, ectopic pregnancy, ovarian torsion, venous thromboembolism and malignant neoplasm and for the important missing information.

Overall, the submitted RMP was considered acceptable by OMSM, except for where limited information and important missing information about the use of corifollitropin alfa exists:

- Combination with a GnRH agonist protocol.
- Patients with renal impairment.
- Patients having risk factors for high ovarian response.
- Pregnant and lactating women.
- Adult and adolescent males with hypogonadotropic hypogonadism.

It is suggested that the sponsor considers making some provision to pro-actively gain such information. This may take the form of a patient register, the details of which should be agreed with the TGA.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

From a Quality perspective, there are no outstanding issues that prevent registration.

Corifollitropin alfa is a glycoprotein consisting of two non-covalently linked subunits: an alfa subunit and a beta subunit corresponding to that of human FSH extended with a C-terminal peptide (CTP) corresponding to the beta subunit of hCG. Elonva is presented as a solution for subcutaneous injection in a pre-filled syringe for single use. Two dosage forms have been developed: 100 µg and 150 µg.

Two pharmacokinetic studies are discussed in the bioavailability/pharmacokinetic report. Study **38803** is a randomised, open label, two way crossover, pharmacokinetic study in healthy, female, pituitary suppressed volunteers conducted to assess the absolute bioavailability of a single dose of 100 µg corifollitropin alfa after subcutaneous injection. 16 healthy females (age range 18-37) participated. All received a single intravenous dose (IV) and 15 subjects received a single subcutaneous dose (SC). The pharmacokinetic results were detailed (see *Biopharmaceutics* above).

Study **33823** is an open label, single centre, cross over study conducted to compare the pharmacokinetics of two corifollitropin alfa formulations in healthy, female subjects whose pituitary function was suppressed with Marvelon (ethinyloestradiol 30 µg, desogestrel 150 µg). Sixteen healthy females were recruited. This study showed that the old and new formulations were not bioequivalent in terms of AUC. The clinical evaluator states that because of this, the studies conducted with the older formulation were considered exploratory studies.

Corifollitropin alfa is derived from a CHO cell line (CHO-K1). The cell line has been suitably characterised and stable. Cell banking processes were satisfactory. Fermentation and purification (viral/prion safety) issues were considered satisfactory.

All manufacturing processes have been validated and batch analyses showed consistency of manufacture.

All chemistry and quality control issues have been resolved. Process and product derived impurities were shown to be at acceptable levels and adequately controlled.

The drug substance release specifications (which include tests for identity, purity and impurities, potency, quantity and general attributes) are acceptable and justified.

The stability data support a shelf life of 24 months at 2-8 ^{0}C in the dark with excursions to less than 30 ^{0}C for no more than 30 days.

The evaluator recommends that as a condition of registration, the first five batches of Elonva be submitted for testing by the TGA and also the manufacturer's release data be approved by the TGA.

Nonclinical

The nonclinical evaluator mentions that an adequate package with GLP compliant studies was submitted. The studies used a product that used a different manufacturing process to that which is proposed for marketing. However, bridging pharmacokinetic studies confirmed that toxicity would be similar to the "proposed formulation".

In comparison to rFSH, corifollitropin alfa had comparable binding affinity to human FSH receptor, was weaker (approximately 1.5 to 2 fold) at producing a signal from the receptor, and had superior *in vivo* activity (probably due to longer half life). It showed high receptor specificity. There was no binding exhibited at concentrations over 1000 times that of the maximum recommended human dose (MRHD) at the LH receptor; there was no bioactivity at concentrations approximately 25 times (MRHD) at the TSH receptor.

Pharmacokinetic studies showed slow absorption, slow elimination, low volume of distribution and low elimination and dose linearity. Bioavailability of a sc dose was approximately 58% in humans, 45% in rats and 85% in dogs. Approximately 90% of corifollitropin alfa was excreted via urine.

Single dose toxicity studies (AUC about 12-13 times that of MRHD) were conducted in mice and rats. There were no deaths reported in rats and the findings were consistent with the pharmacology of corifollitropin alfa. In mice there was some hepatotoxicity seen. There was no cardiovascular toxicity at exposures 250 times MRHD in relation to AUC, after a single SC dose in dogs.

Repeat dose studies (13 week) were conducted in rats and dogs. There was a 39 week study also conducted in male dogs. Exposure ratios achieved in repeat dose studies were considered to be adequate. In female rats the changes in the ovaries were indicative of either stimulation or non stimulation/ inhibition (the latter appeared to reflect antibody neutralisation of both drug and endogenous FSH). Uterus, vagina and mammary glands were affected in females of both species. Female dogs also showed changes in adrenals, skin, skeletal muscles, and reduction in red cell parameters, thrombocytopenia and increase in cholesterol. These changes were due to secondary effect of increases in oestrogen or progesterone. Pituitary function was affected in female rats probably due to neutralisation of endogenous FSH by anti-corifollitropin antibodies. Most of these changes were seen with rFSH also. These events were reversible or were expected to return to baseline once therapy ceased.

Genotoxicity studies were negative; there were no carcinogenicity studies conducted and this was considered acceptable.

Reproductive toxicity studies were performed in rats and rabbits. The findings suggest that it would be appropriate to recommend that corifollitropin alfa be contraindicated in pregnancy.

Teratogenicity was observed in rabbits that superovulated.

Overall, the nonclinical evaluator recommends approval.

Clinical

Pharmacodynamics

Three studies are discussed. The preliminary Study, **38801**, showed a rise in inhibin –B levels in hypogonadal male patients which rose to a peak around Day 6 and then returned to baseline levels by day 28, which was the time for the next injection. No significant change in testosterone or oestradiol levels was found.

Study **38802**, a Phase I study on 24 healthy females used doses of 15, 30, 60 and 120 µg. The median follicle size of 15 and 27 mm were observed in the 60 and 120 µg groups. Significant increases were also observed in relation to inhibin- B levels in these two dose groups.

Study **38823** compared the old formulation with the "to be marketed" formulation using 120 µg dose strength. The number of follicles > 5mm observed on the day of maximum response was 8 (7-11) with the old formulation and 10 (7-15) with the new formulation. The rise in

inhibin- B was more sustained with the new formulation. This response was maintained over 10 days.

Pharmacokinetics. It should be noted that the earlier studies (Phase 1 and Phase II) used the non protein free (non- pf) formulation. Later studies used the protein free (pf) formulation.

The same three studies contributed pharmacokinetic data. In the preliminary Study, **38801**, the C_{max} was 0.43 ± 0.12 ng/mL, t_{max} 46 ±18 h and $t_{1/2}$ 95 ± 26h. The evaluator mentions that Study **38802** showed similar values.

Study **38823** was a bioequivalence study comparing the old (non pf) versus new (pf) formulation. This was an open label crossover study conducted in 16 healthy females whose pituitary function was suppressed by Marvelon ® (ethinyloestradiol 30 µg and desogestrel 150µg). A dose of 120 µg was used. The formulations were not bioequivalent in terms of AUC. The new formulation yielded 17- 20% more exposure. For this reason, the studies that used the non-pf formulation were considered exploratory studies.

Study 38803 was an absolute bioavailability study which was of an open crossover design using 16 healthy females-100 µg was used intravenously or subcutaneously. The absolute bioavailability was 58%.

The clinical evaluator discussed the pharmacokinetics derived from three major studies (**38826**-dose ranging, **107012, 38819**-pivotal). Two other studies using the non- pf are also considered supportive. The main observations from these studies are:

1) T_{max} is approximately 41 to 44 hours and $t_{1/2}$ is 64- 74 hours. The latter is much longer than that which is reported for other FSH products (FSH; 12 hours and Puregon®; 40 hours).
2) Dose normalised C_{max} and AUC in studies **38819** and **38826** were consistent. Exposure was higher in Study **107012** and was attributable to lower body weight of the subjects in that study.
3) Between individual variation is high being greater than 30%. Whilst this is addressed in relation to body weight/ ethnicity, other factors causing variance are not identified. Excessive variance in exposure with this product is a concern because of the potential to cause OHSS. This appears to be addressed in the PI in *Precautions* section where regular ultrasonic assessments of follicular development and/ or determination of serum oestradiol levels are recommended.
4) Studies using the non- pf formulation (38805 and 38807) confirmed dose proportionality within each study.

Efficacy:

The clinical evaluator briefly discussed Study **38805**. This study is considered to be of limited relevance because the dose, formulation and study population were irrelevant to this submission.

The clinical evaluator also discussed the standard controlled ovarian stimulation protocol. A single injection of corifollitropin alfa was given to initiate treatment in the "short protocol" COS. [This protocol refers to administering FSH for 10 days commencing at the beginning of the menstrual cycle to induce follicular growth, a GnRH antagonist to prevent premature endogenous LH surge and ovulation, then hCG to trigger ovulation]. The comparator was the standard rFSH administered daily for 7 days. From Day 8, subjects in both treatment groups received daily 150 units of rFSH till hCG could be administered. Luteal phase support was left to the investigator's practice.

Study **38807** was a dose ranging Phase II study conducted to assess the dose of corifollitropin alfa required to initiate follicular development in patients undergoing controlled ovarian stimulation. This study used the earlier formulation (non pf) and its findings formed the dose selection for subsequent studies. This study was conducted in two stages. The initial stage was an exploratory study involving 6 subjects. The first two subjects received a single dose of 120 µg corifollitropin alfa and since there was no follicular development, the next four subjects received 180 µg. Oocytes were retrieved in all patients. The second stage included 120 µg, 180 µg and 240 µg corifollitropin alfa; this was administered to 25 subjects (each group). A fourth group received 150 µg rFSH daily. The primary efficacy parameter was the total dose of rFSH required (from Day 8 of the cycle) to achieve the criteria for hCG administration. As seen in Table 6 above.

The secondary efficacy endpoint also included the number of cumulus –oocyte complexes recovered. The findings were similar to the primary efficacy endpoint.

Study **38826** was an open label Phase II study using the pf formulation. The protocol and inclusion criteria were similar to the previous study. 325 subjects were randomised and 315 were treated. 77 were treated with the 60 µg dose, 77 were treated with 120 µg and 79 with the 180 µg dose. A control group of 82 subjects was treated with 150 IU rFSH (Puregon®) daily. The primary efficacy parameter was the number of cumulus-oocyte complexes retrieved. There was a clear dose response seen in relation to this endpoint. The mean (SD) number of cumulus-oocyte complexes recovered per started cycle were 5.2 (5.5) in the 60 µg group (N=78); 10.3 (6.3) in the 120 µg group (n=77); 12.5 (8.0) in the 180 µg (n=79); and 7.7 (6.3) in the 150 IU Puregon® group (n=81). The clinical evaluator also mentions that the size distribution varied with the dose of corifollitropin alfa. On Day 8, the mean number ≥ 11mm in diameter were 6.8, 10.1 and 12.8 with increasing doses of corifollitropin alfa and 7.8 mm with Puregon®.

The evaluator mentions that dose response was seen in relation to duration and the amount of rFSH given from Day 8 onwards. The median duration of treatment from Day 8 to hCG administration was 4, 3, 2 days for the 60, 120 and 180 µg corifollitropin alfa doses and 2 days for the Puregon® treated group. Median total rec FSH was 600 IU, 450 and 300 for the corifollitropin alfa groups and 1350 IU for the Puregon® treated group. Dose response was also seen in relation to serum E2 and inhibin B levels. The evaluator concludes that (based on these data), the optimal dose was more likely to be between 60 -120 µg than between 120-180 µg.

Phase III studies: (Two completed studies: **107012** and **38819**. One ongoing Study **38825**)

Study **107012** is a Phase III, multicentre, randomised, double blind active controlled study using a single 100 µg corifollitropin alfa using the common COS protocol described earlier. Subjects with normal menstrual cycle undergoing COS, with body weight ≤ 60 kg were eligible to be recruited from two Asian and seven European sites; 396 subjects were randomised and treated. Of these, 268 were in the corifollitropin alfa group and 128 in the rFSH group.

This was designed as an equivalence study. The primary endpoint for this purpose was the number of oocytes retrieved in each group; the predefined margin was (-3, +5). The evaluator is of the opinion that the rationale for the specified margin was based on "sound clinical reasoning and appears valid".

The results of the primary and secondary efficacy parameters (ITT) are shown in Table 9. The mean (SD) number of cumulus-oocyte-complexes retrieved per cycle in the ITT group was 13.3 (7.3) versus 10.6 (5.9) in the Puregon® group. The estimated treatment difference

was 2.5 in favour of corifollitropin alfa with a 95% CI of 1.2, 3.9, this being within the pre-defined range.

Ongoing pregnancy rate was a secondary efficacy endpoint. In the ITT population the difference was -9.2 (-18.9, 0.5), thus favouring the reference treatment. Though the difference of 9% and the lower bound of -19% appears large, there were no obvious explanation for this finding.

The evaluator concludes that the "study yields a robust finding of efficacy for the applicant product being equivalent to comparator for its intended purpose of stimulation of ovulation".

Study **38819** was a multicentre, randomised double blind "non inferiority study" where the subjects were randomised on 1: 1 basis. This study used a similar protocol to **107012**, however the females weighed between 60 kg and≤ to 90kg. 150 µg of corifollitropin alfa was used and 200 IU rFSH was the comparator.

There were two primary endpoints: (1). Ongoing pregnancy rate assessed at least 10 weeks after embryo transfer (requested by the FDA) and (2). Number of oocytes retrieved (requested by the EMA).

Ongoing pregnancy rate was the primary endpoint on which the comparison of non-inferiority was based and -8% was set for the lower bound of the two sided 95% CI. This was considered acceptable as there is a difference of 10% between clinical routine pregnancy rates per ART cycles in Europe and USA. A sample size of at least 1380 subjects was the minimum requirement to demonstrate non-inferiority using an 8% margin, assuming a pregnancy rate could not exceed 30%. In addition, predefined margins of -3,+5 were used for the bounds of 95% CI for the difference between the treatment groups in numbers of retrieved oocytes on the basis of equivalence testing. Thus, both non- inferiority and equivalence testing have been used for separate parameters; the clinical evaluator questions the suitability of this. However, the clinical evaluator states that equivalence in relation to both endpoints would have been demonstrated had it been pre-specified.

757 subjects were randomised to receive corifollitropin alfa and 752 subjects to rFSH. The results are tabulated in Table 11 above.

The difference in the treatment groups for ongoing pregnancy rates in the ITT were 0.9% (3.9;5.7) establishing non-inferiority with adequate power. In case of the number of oocytes retrieved the difference was 1.2, (0.5, 1.9), where equivalence was established.

Study **38825** is an uncontrolled, multicentre, open label trial using corifollitropin alfa in the common COS protocol. Treatment was corifollitropin alfa 150 µg was planned for three cycles and efficacy data collected after the first cycle. The clinical evaluator states that the results (cumulus oocyte complexes retrieved) were similar to those observed in the pivotal efficacy studies.

The influence of demographics and physical attributes of the subjects were also discussed by the clinical evaluator. It appears that body weight is a determinant of drug exposure and this has been addressed in the draft PI. Influence of other factors was not considered clinically significant.

Overall, the evaluator mentions that treatment with corifollitropin alfa was comparable with chosen reference of 150 units of rFSH daily (200 units in Study **38819**). The clinical evalauator concludes that the reference treatment was appropriate in most cases. The protocol allowed for individual adjustment of dosage; also any minor difference in efficacy could be dealt with by adjusting the dosage of gonadotropins in the remaining 2-4 day period before hCG administration.

Safety (20-27).

A total of 2185 subjects received at least 1 dose of corifollitropin alfa. Of these, 309 received a single dose of 100 µg (mostly in Study **107012**). The evaluator states that the majority (n=1107) received 150 µg. Of these, 681 received 1 dose, 321 received two doses and 105 subjects received three doses.

As seen in Table 13 above, OHSS was slightly higher in **107012** with corifollitropin alfa but similar to rFSH in Study **38819**. The evaluator is critical of the exclusion of patients with history of OHSS or at risk of OHSS, however mentions that this is addressed in the draft PI (see Precautions).

In relation to immunogenicity, blood samples were obtained and screened with the anti-corifollitropin alfa assay from 97.4% subjects in Phase I, 92.6% in Phase II and from 98.7% subjects in Phase III studies. There were no positive results in the Phase I and II subjects. There were three subjects who had positive assays in Phase III studies; they had low levels which were neutralised by the addition of corifollitropin alfa or FSH. All three had normal ovarian response to corifollitropin alfa and two became pregnant. Subsequent samples showed negative results in relation to the binding assay.

There were no reports of moderate to severe redness, itching swelling or pain. Mild reactions were similar in both groups.

The evaluator mentions that pooled data for the Phase II (38817, 38827 which are follow up studies of 38805/38807 and 38826) studies in relation to pregnancy and neonatal outcomes were provided. In these studies, there were excess adverse events in the corifollitropin alfa group. However the numbers were small and this trend was not reflected in the Phase III studies. Pooled data from studies 38834, 38821, 107014 and 38829 showed that there was no difference in either maternal or foetal events between the two groups.

There were no significant effects seen in relation to laboratory investigations.

Overall, the clinical evaluator concludes that there were no unexpected safety issues with the data set. The potential hazards of using a fixed dose regimen with corifollitropin alfa are addressed in the *Precautions* sections of the draft PI.

Overall, the clinical evaluator recommends registration and ongoing safety monitoring for unexpected receptor interaction or other effects that could arise.

Risk-Benefit Analysis

Delegate's comments and recommendation:

1. The advantage of corifollitropin alfa in COS is that it would be more convenient than the daily injections of rFSH. There has been no objective measure of convenience, however.
2. Corifollitropin alfa has been shown to be equivalent/ non inferior to rFSH that is administered daily in terms of the efficacy endpoints. However, in Study **107012**, there is a suggestion that the dose used may have been higher than required, based on the slightly higher incidence of OHSS. It may be that a lower dose of corifollitropin would have been optimal in terms of OHSS- the sponsor should comment on this, in its pre-Advisory Committee on Prescription Medicines (ACPM) response.
3. The main risk with a fixed dose regimen (as proposed with corifollitropin alfa) is the potential to cause OHSS. This was similar to the comparator products in the pivotal studies. This is also addressed in the PI.

Overall, the efficacy and safety data are adequate to approve for registration.

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

1. The ACPM recommended approval of the submission from Schering-Plough Pty Ltd to register a new chemical entity, corifollitropin alfa (Elonva) solutions for injection 100 µg / 0.5 mL and 150 µg / 0.5 mL for the indication:

> Controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women participating in *in vitro* fertilisation techniques.

In making this recommendation the ACPM agreed with the delegate that safety and efficacy had been demonstrated for the proposed indication. However, the ACPM expressed concern that safety risks associated with ovarian hyper-stimulation syndrome (OHSS), particularly in patients with polycystic ovarian syndrome, had not been adequately addressed in the Product Information. The ACPM further advised that the guidance on appropriate dosage regimens to match the age of the target population should be strengthened.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Elonva corifollitropin alfa 150 micrograms/0.5mL solution for injection prefilled syringe and Elonva corifollitropin alfa 100 micrograms/0.5mLsolution for injection prefilled syringe for single subcutaneous injection (100µg for ≤60kg and 150µg for >60kg), indicated for:

> Controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing *in vitro* fertilisation techniques.

References (nonclinical)

Beitins, I.Z., Derfel, R.L., O'Loughlin, K. and McArthur, J.W. (1977) Immunoreactive luteinizing hormone, follicle stimulating hormone and their subunits in human urine following gel filtration. *J. Clin. Endocrinol*. Metab. 44, 149-159.

Emmanouel, D.S., Stavropoulos, T. and Katz, A.I. (1984) Role of the kidney in metabolism of gonadotropins in rats. *Am. J. Physiol*. 247, E786-E792.

Fujimoto, S., Pahlavan, N. and Dukelow, W.R. (1974) Chromosome abnormalities in rabbit preimplantation blastocysts induced by superovulation. *J. Reprod. Fert*. 40, 177-181.

Geil, R.G. and Lamar, J. K. (1977) FDA studies of estrogen, progestogens and estrogen/ progestogen combination in the dog and monkey. *J. Toxicol. Environ. Health* 3, 179-193.

Geurts, T.B.P., Peters, M.J.H., van Bruggen, J.G.C., de Boer, W. and Out, H.J. (1996) PUREGON® (Org 32489) - recombinant human follicle-stimulation hormone. Drugs Today 32, 239-258.

Günzel, P., Putz, B., Lehmann, M., Hasan, S.H., Hümpel, M. and El Etreby, M.F. (1989) Steroid toxicology and the 'pill'. Comparative aspects of experimental test systems and the human. In: Advances in Applied Toxicology, eds, Dayan, A.D. and Paine, A.J. 19-49.

Johnson, A.N. (1989) Comparative aspects of contraceptive steroids – effects observed in Beagle dogs. *Toxicol. Path*., 17, 389-395.

Maier, W.E. and Herman, J.R. (2001) Pharmacology and toxicology of ethinyl estradiol and norethindrone acetate in experimental animals. *Regulatory Toxicol. and Pharmacol*., 34, 53-61.

Matzuk, M.M., Hsueh, A.J.W., Lapolt, P., Tsafriri, A., Keene, J.L. and Boime, I.(1990) The biological role of the carboxyl-terminal extension of human chorionic gonadotropin β-subunit. *Endocrinol*. 126, 376-383.

Nisula, B.C., Blithe, D.L., Akar, A., Lefort, G. and Wehmann, R.E. (1989) Metabolic fate of human choriogonadotropin. *J. Steroid Biochem.*, 33, 733-737.

Roberts, R., Iatropoulou, A., Ciantar, D., Stark, J., Becker, D.L., Franks, S. and Hardy, K. (2005) Follicle-stimulating hormone affects metaphase I chromosome alignment and increases aneuploidy in mouse oocytes matured *in vitro*. *Biol. Reprod.*, 72, 107-118.

Seibert, B and Günzel, P. (1994) Animal toxicity studies performed for risk assessment of the once-a-month injectable contraceptive Mesigyna®. *Contraception*, 49, 303-333.

Ulloa-Aguirre, A, Uribe, A. ; Zarinan, T.; Buston-Jaimes, I., Perez-Solis, M. A. and Dias, J. A. (2007) Role of the intracellular domains of the human FSH receptor in $G_{\alpha S}$ protein coupling and receptor. *Molec. and Cellular Endocrinology*, 260-62, 153-162.

Vogel, R. and Speilmann, H. (1992) Genotoxic and embryotoxic effects of gonadotrophin-hyperstimulated ovulation of murine oocytes, preimplantation embryos, and term fetuses. *Reprod. Toxicol.*, 6, 329-333.

Wiik, A. (2008) Estrogen receptors in skeletal muscle. Expression and activation. Doctoral thesis, Karolinka Institutet.

Zambrano, E., Zariñán, T., Olivares, A., Barrios-de-Tomasi, J. and Ulloa-Aguirre, A. (1999) Receptor binding activity and *in vitro* biological activity of the human FSH charge isoforms as disclosed by heterologous and homologous assay systems. *Endocrine* 10, 113-121.

Zayed, I., van Esch, E. and McConnell, R.F. (1998) Systemic and histopathologic changes In beagle dogs after chronic daily oral administration of synthetic (ethinyl estradiol) or natural (estradiol) estrogens, with special reference to the kidney and thyroid. *Toxicol. Pathol.*, 26, 730-741.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

ELONVA®

Corifollitropin alfa (rch)

NAME OF THE DRUG

Corifollitropin alfa solution for injection

Corifollitropin alfa, a gonadotrophin designed as a sustained follicle stimulant is a glycoprotein consisting of two non-covalently linked non-identical subunits called α and β. The α-subunit is identical to that of human follicle-stimulating hormone (FSH); the β-subunit is composed of the complete β-subunit of human FSH (residues 1-111) extended with the carboxy-terminal peptide (CTP) of the β–subunit of human chorionic gonadotrophin (hCG) (residues 118-145). *CAS No.:* 195962-23-3.

α-subunit

```
APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP
            *                           *
LRSKKTMLVQ KNVTSESTCC VAKSYNRVTV MGGFKVENHT

ACHCSTCYYH KS
```

β-subunit

```
      *                     *
NSCELTNITI AIEKEECRFC ISINTTWCAG YCYTRDLVYK

DPARPKIQKT CTFKELVYET VRVPGCAHHA DSLYTYPVAT
                                   &&
QCHCGKCDSD STDCTVRGLG PSYCSFGEMK ESSSSKAPPP
&     &       & &
SLPSPSRLPG PSDTPILPQ
```

* = N-glycosylation sites

& = O-glycosylation sites

Corifollitropin alfa is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, using a chemically defined cell culture medium without the addition of antibiotics, human- or animal-derived proteins (protein-free) or any other components of human or animal origin.

DESCRIPTION

Elonva is presented as a sterile, ready for use, clear and colourless aqueous solution for subcutaneous administration. Each pre-filled syringe contains 100 micrograms or 150 micrograms of corifollitropin alfa in 0.5 mL. Elonva also contains the excipients sodium citrate, sucrose, polysorbate 20, methionine, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and Water for Injections.

Elonva contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially 'sodium-free'.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic Group: gonadotrophins

WHO-proposed ATC code: G03GA09 corifollitropin alfa.

Corifollitropin alfa has the same pharmacodynamic profile as (rec)FSH, but with a markedly prolonged duration of FSH activity, achieved by the addition of the (CTP) of hCG to the β-subunit of human FSH. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of Elonva may replace the first seven injections of any daily (rec)FSH preparation in a COS treatment cycle. Corifollitropin alfa does not display any intrinsic luteinising hormone (LH)/hCG activity.

Pharmacokinetics

Corifollitropin alfa has an elimination half-life of 69 hours (59 – 79 hours[1]). After administration of the recommended dose, serum concentrations of corifollitropin alfa are sufficient to sustain multiple follicular growth for an entire week. This justifies replacement of the first seven injections of daily (rec)FSH with a single subcutaneous injection of Elonva in COS for the development of multiple follicles and pregnancy in women undergoing *in vitro* fertilisation techniques (see DOSAGE AND ADMINISTRATION).

After a single subcutaneous injection of Elonva, maximum serum concentrations of corifollitropin alfa are reached after 44 hours (34 – 57 hours[1]). The absolute bioavailability is 58% (48 – 70%[1]).

The steady state volume of distribution and clearance are 9.2 L (6.5 – 13.1 L[1]) and 0.13 L/h (0.10 – 0.18 L/h[1]), respectively. The pharmacokinetic properties of corifollitropin alfa are independent of the administered dose over a wide range (7.5 – 240 micrograms). [[1] Predicted range for 90% of subjects.]

Body weight is a determinant of exposure to corifollitropin alfa. In clinical studies, serum concentrations of corifollitropin alfa were similar after administration of 100 micrograms corifollitropin alfa to women with a body weight ≤ 60 kilograms and of 150 micrograms corifollitropin alfa to women with a body weight > 60 kilograms.

Distribution, metabolism and elimination of corifollitropin alfa are very similar to other gonadotrophins, such as FSH, hCG and LH. After absorption into the blood, corifollitropin alfa is distributed mainly to the ovaries and the kidneys. Elimination of corifollitropin alfa predominantly occurs via the kidneys and may be impaired in patients with renal insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Hepatic metabolism contributes to a minor extent to the elimination of corifollitropin alfa. Although data in hepatically impaired patients are not available, hepatic impairment is unlikely to affect the pharmacokinetic profile of corifollitropin alfa.

CLINICAL TRIALS

The efficacy and safety of Elonva was evaluated in two pivotal phase III comparative trials with recFSH (Trials 38819 and 107012) and an uncontrolled multicycle trial (Trial 38825).

The two comparative clinical trials used similar inclusion criteria (except for the difference in body weight): females of couples with an indication for COS and IVF or ICSI; ≥ 18 and ≤ 36 years of age at the time of signing informed consent; Body weight > 60 and ≤ 90 kg and BMI ≥ 18 and ≤ 32 kg/m^2 (Study 38819); body weight ≤ 60 kg and BMI ≥ 18 and ≤ 32 kg/m^2 (Study 107012); normal menstrual cycle length: 24-35 days; availability of ejaculatory sperm (use of donated and/or cryopreserved sperm was allowed).

Compared to the general IVF population the main subgroups of patients excluded were: (1) patients with a history of non- or low ovarian response; (2) patients with more than three unsuccessful IVF cycles since the last established ongoing pregnancy; (3) patients with a history of hyper-response or OHSS; (4) patients with polycystic ovarian response (PCOS); and (5) patients with a basal antral follicle count above 20.

Trial 38819

In this double-blind, randomized, active-controlled, non-inferiority trial, women weighing >60 kg and ≤90 kg received a single subcutaneous injection of 150 micrograms Elonva on day 2 or 3 of the menstrual cycle (Stimulation Day 1). A second group of subjects received daily injections of 200 IU recFSH. From Stimulation Day 8 onwards, treatment continued with daily recFSH injections. The median duration of stimulation was 9 days for both treatment groups (up to and including the day of hCG stimulation). The GnRH antagonist ganirelix (0.25mg) was administered with daily subcutaneous injections starting on Stimulation Day 5 up to and including the Day of hCG. As soon as three follicles ≥17 mm were observed by ultrasonography, hCG (10,000 or 5,000 IU) was administered to induce final oocyte maturation.

The study population consisted of 1,506 treated patients with a mean age of 31.5 years and a mean body weight of 68.6 kg. The primary endpoint of the trial was ongoing pregnancy rate assessed at least 10 weeks after embryo transfer. The number of oocytes retrieved was analysed as the co-primary endpoint.

The results obtained for ongoing pregnancy rates are presented in Table A and the results for the number of oocytes retrieved are presented in Table B.

Table A

Primary efficacy variable	Trial 38819 Body weight > 60 kg	
	150 micrograms Elonva (N=756)	200 IU recFSH (N=750)
Ongoing pregnancy rate (%)*	38.9	38.1
Difference [95% CI]	0.9 [-3.9; 5.7]	

* Per started cycle

A single subcutaneous injection of 150 micrograms Elonva for the first seven days of controlled ovarian stimulation (COS) was non-inferior to a daily dose of 200 IU recFSH with respect to ongoing pregnancy rates (38.9% versus 38.1%, respectively). The estimated treatment difference in ongoing pregnancy rates of 0.9% was entirely within the -8% non-inferiority margin (Table A).

Trial 107012

In this multicenter, randomized, double-blind, active-controlled, equivalence trial, women weighing 60 kg or less, received a single subcutaneous injection of 100 micrograms Elonva on day 2 or 3 of the menstrual cycle (Stimulation Day 1). A second group of subjects received daily injections of 150 IU recFSH. From Stimulation Day 8 onwards, treatment continued with daily recFSH injections (maximally 200 IU). The median duration of stimulation was 9 days for both treatment groups (up to and including the day of hCG stimulation). The GnRH antagonist ganirelix (0.25 mg) was administered with daily subcutaneous injections starting on Stimulation Day 5 up to and including the Day of hCG. As soon as three follicles $\geq$ 17 mm were observed by ultrasonography, hCG (10,000 or 5,000 IU) was administered to induce final oocyte maturation.

The study population consisted of 396 treated patients with a mean age of 30.0 years and a mean body weight of 54.2 kg. The primary efficacy end point of the study was the number of oocytes retrieved. The results obtained for the number of oocytes retrieved are presented in Table B together with the number of oocytes retrieved in Trial 38819.

Table B

Primary efficacy variable	Trial 107012 Body weight ≤ 60 kg		Trial 38819 Body weight > 60 kg	
	100 micrograms Elonva (N=268)	150 IU recFSH (N=128)	150 micrograms Elonva (N=756)	200 IU recFSH (N=750)
Mean number of oocytes retrieved*	13.3	10.6	13.7	12.5
Difference [95% CI]	2.5 [1.2; 3.9]		1.2 [0.5; 1.9]	
	p < 0.001		p = 0.001	

* Per started cycle

Treatment with 100 micrograms Elonva (Trial 107012) or 150 micrograms Elonva (Trial 38819), for the first seven days of COS resulted in a significantly higher number of retrieved oocytes compared to treatment with a daily dose of 150 or 200 IU of recFSH, respectively. However, the difference was within the predefined equivalence margins.

In the two comparative clinical trials, the safety profile of a single injection of Elonva was comparable to daily injections with recFSH. The Ovarian Hyperstimulation Syndrome (OHSS) incidence reported for Elonva was slightly higher than for recFSH, but the difference was small and not statistically significant.

Trial 38825

In this multicenter, open-label, uncontrolled trial the non-immunogenicity and overall safety and efficacy of Elonva was assessed in women with a body weight > 60 kg undergoing up to three COS cycles. Each cycle started with a single subcutaneous injection of 150 micrograms Elonva on day 2 or 3 of the menstrual cycle. From stimulation day 8, treatment was continued with daily (rec)FSH (maximally 225 IU). The GnRH antagonist (ganirelix or cetrorelix) was administered with daily subcutaneous injections starting on Stimulation Day 5 or 6 up to and including the Day of hCG. As soon as three follicles ≥ 17 mm were observed by ultrasonography, (rec)hCG (5,000-10, 000 IU / 250 micrograms) was administered to trigger final oocyte maturation.

The study population consisted of 682 patients starting in the first COS cycle, with a mean age of 32.9 years and a mean body weight of 67 kg. The main study end points were: antibody formation against corifollitropin alfa; hypersensitivity reactions; local tolerance at the injection site; occurrence of (serious) adverse events ((S)AEs); and efficacy in terms of the number and quality of oocytes and embryos and the ongoing pregnancy rates.

The results of this study show that a single injection of 150 micrograms Elonva can safely and effectively initiate and sustain ovarian stimulation during the first 7 days of COS prior to IVF/ICSI in patients undergoing up to 3 cycles of treatment, without concerns related to immunogenicity.

INDICATIONS

Controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing *in-vitro* fertilisation techniques.

CONTRAINDICATIONS

- Tumours of the ovary, breast, uterus, pituitary or hypothalamus.
- Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause.
- Primary ovarian failure.
- Ovarian cysts or enlarged ovaries.
- A history of Ovarian Hyperstimulation Syndrome (OHSS).
- A previous COS cycle that resulted in more than 30 follicles ≥ 11 mm measured by ultrasound examination.
- A basal antral follicle count > 20.
- Fibroid tumours of the uterus incompatible with pregnancy.

- Malformations of the reproductive organs incompatible with pregnancy.
- Pregnancy or lactation (see PRECAUTIONS).
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

- Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, women should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.
- Elonva is intended for single subcutaneous injection only. Additional injections of Elonva should not be given within the same treatment cycle.
- In the first seven days after administration of Elonva, no (rec) FSH should be administered (see DOSAGE AND ADMINISTRATION).
- In patients with renal insufficiency the excretion of corifollitropin alfa might be impaired. Therefore, the use of Elonva in these women is not recommended.
- There are limited data on the use of Elonva in combination with a Gonadotrophin Releasing Hormone (GnRH) agonist. Results of a small uncontrolled study suggest a higher ovarian response than in combination with a GnRH antagonist. Therefore, the use of Elonva is not recommended in combination with a GnRH agonist (see DOSAGE AND ADMINISTRATION).
- Elonva has not been studied in patients with polycystic ovarian syndrome (PCOS). In these women the use of Elonva is not recommended.
- The ovarian response was shown to be higher after treatment with Elonva than after treatment with daily recFSH. Therefore, patients with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Elonva. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, careful monitoring for potential ovarian hyperresponse is recommended.
- *Ovarian Hyperstimulation Syndrome (OHSS)*
  OHSS is a medical event distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts (prone to rupture), acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnoea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.

  Signs and symptoms of OHSS are stimulated by administration of human Chorionic Gonadotrophin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotrophin stimulation. Usually, early OHSS resolves spontaneously with the onset of menses. Late OHSS occurs more than 10 days after hCG administration, as a consequence of (multiple) pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

To minimise the risk of OHSS, ultrasonographic assessments of follicular development and/or determination of serum estradiol levels should be performed prior to treatment and at regular intervals during treatment. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter. When there are 30 or more follicles in total it is advised to withhold hCG administration.

Depending on the ovarian response, the following can be used to prevent OHSS:
- withhold further stimulation with a gonadotrophin for a maximum of 3 days (coasting);
- delay triggering final oocyte maturation with hCG administration until estradiol levels stabilize or decrease;
- administer a dose lower than 10,000 IU of hCG for triggering final oocyte maturation, e.g. 5,000 IU hCG or 250 micrograms rec-hCG (which is equivalent to approximately 6,500 IU);
- cryopreserve all embryos for future transfer;
- withhold hCG and cancel the treatment cycle.

For luteal phase support, administration of hCG should be avoided.

Adherence to the recommended Elonva dosage and treatment regimen and careful monitoring of ovarian response is important to minimise the risk of OHSS.

- Multiple pregnancies and births have been reported for all gonadotrophin treatments. The woman and her partner should be advised of the potential risks for the mother (pregnancy and delivery complications) and the neonate (low birth weight) before starting treatment. In women undergoing ART procedures the risk of multiple pregnancy is mainly related to the number of embryos transferred.
- Since infertile women undergoing ART, and particularly IVF, often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. It is important to have early ultrasound confirmation that a pregnancy is intrauterine, and to exclude the possibility of extrauterine pregnancy.
- The incidence 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 the higher incidence of multiple pregnancies.
- There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
- In women with generally recognized risk factors for thromboembolic events, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m^2) or thrombophilia, treatment with gonadotrophins may further increase this risk. In these women the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Use in pregnancy (Category B3)

The use of Elonva during pregnancy is contraindicated. No teratogenic risk has been reported, following controlled ovarian stimulation in clinical use with gonadotrophins. When inadvertent exposure during pregnancy occurs, clinical data are not sufficient to exclude a teratogenic effect of corifollitropin alfa. Administration of corifollitropin alfa to rats and rabbits, prior to and directly after mating, and during early pregnancy, resulted in embryotoxicity. In rabbits, when administered prior to mating, teratogenicity has been observed. Both embryotoxicity and teratogenicity are considered a consequence of the superovulatory state of the animal not able to support a number of embryos above a physiological ceiling. The relevance of these findings for the clinical use of Elonva is limited.

Use in lactation

The use of Elonva during lactation is contraindicated.

Effects on fertility

Corifollitropin alfa administered to rats and rabbits prior to mating did not impair fertility; treatment stimulated the development of multiple follicles

Carcinogenicity

Long-term carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of corifollitropin alfa.

Genotoxicity

Corifollitropin alfa was not mutagenic or clastogenic in the standard battery of tests.

Effect on ability to drive and use machines

No studies on the ability to drive and use machines have been performed.

Elonva may cause dizziness. Patients should be advised that if they feel dizzy, they should not drive or use machines.

Interactions with other medicines

No interaction studies with Elonva and other medicines have been performed. Since corifollitropin alfa is not a substrate of cytochrome P450 enzymes, no interactions with other medicinal products are anticipated.

ADVERSE EFFECTS

The most frequently reported adverse drug reactions during treatment with Elonva in clinical trials are OHSS (5.2%), pelvic pain (4.1%) and discomfort (5.5%), headache (3.2%), nausea (1.7%), fatigue (1.4%) and breast complaints (including tenderness) (1.2%).

The table below displays the main adverse drug reactions in women treated with Elonva in clinical trials according to body system and frequency.

Body system	Frequency	Undesirable effect
Nervous system disorders	Common (≥ 1%, < 10%)	Headache
	Uncommon (≥ 0.1%, < 1%)	Dizziness
Gastrointestinal disorders	Common (≥ 1%, < 10%)	Nausea
	Uncommon (≥ 0.1%, < 1%)	Abdominal pain, vomiting, diarrhoea, constipation and abdominal distension
Reproductive system and breast disorders	Common (≥ 1%, < 10%)	OHSS, pelvic pain and discomfort, breast complaints
	Uncommon (≥ 0.1%, < 1%)	Ovarian torsion
General disorders and administration site conditions	Common (≥ 1%, < 10%)	Fatigue

In addition, ectopic pregnancy, miscarriage and multiple gestations have been reported. These are considered to be related to the ART procedure or subsequent pregnancy.

DOSAGE AND ADMINISTRATION

Treatment with Elonva should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

Elonva may be administered by the woman herself or her partner, provided that proper instructions are given by the physician. Self administration of Elonva should only be performed by women who are well-motivated, adequately trained and with access to expert advice.

Do not use if the solution contains particles or if the solution is not clear.

In women with a body weight ≤ 60 kilograms a single dose of 100 micrograms should be administered.
In women with a body weight > 60 kilograms a single dose of 150 micrograms should be administered.

Stimulation day 1:
Elonva should be administered as a single subcutaneous injection, preferably in the abdominal wall, during the early follicular phase of the menstrual cycle.

The recommended doses of Elonva have only been established in a treatment regimen with a GnRH antagonist (see PRECAUTIONS).

Stimulation day 5 or 6:
Treatment with Gonadotrophin Releasing Hormone (GnRH) antagonist should be started on stimulation day 5 or day 6 depending on the ovarian response, i.e the number and size of growing follicles and/or the amount of circulating oestradiol. The GnRH antagonist is used to prevent premature Luteinising Hormone (LH) surges.

Stimulation day 8:
Seven days after the injection with Elonva, treatment may be continued with daily injections of (rec)FSH until the criteria for triggering final oocyte maturation (3 follicles ≥ 17 mm) have been reached. The daily dose of (rec)FSH may depend on the ovarian response. In normal responders a daily dose of 150 IU (rec)FSH is advised. Administration of (rec) FSH on the day of human Chorionic Gonadotrophin (hCG) administration can be omitted, depending on the ovarian response. In general, adequate follicular development is achieved on average by the ninth day of treatment (range 6 to 18 days).

As soon as three follicles ≥ 17 mm are observed, a single injection of 5,000 up to 10,000 IU hCG is administered the same day or the day thereafter to induce final oocyte maturation. In case of an excessive ovarian response, see the recommendation given in PRECAUTIONS in order to minimise the risk for developing ovarian hyperstimulation syndrome (OHSS).

Special populations
Renal impairment: No clinical studies have been performed in patients with renal insufficiency. Since the elimination of corifollitropin alfa might be impaired in patients with renal insufficiency, the use of Elonva in these women is not recommended (see PRECAUTIONS).

Hepatic impairment: Although data in hepatically impaired patients are not available, hepatic impairment is unlikely to affect the elimination of corifollitropin alfa (see Pharmacokinetics).

Incompatibilities
In the absence of compatibility studies, the solution for injection must not be mixed with other medicinal products.

OVERDOSAGE

More than one injection of Elonva within one treatment cycle or too high a dose of Elonva and/or (rec)FSH are likely to increase the risk of OHSS (see PRECAUTIONS). For measures to prevent and manage OHSS see PRECAUTIONS.

PRESENTATION

Elonva 100 micrograms/ 0.5mL

Elonva 150 micrograms/0.5mL

Elonva is supplied in disposable 1-mL luerlock syringes of hydrolytic glass (type I), closed with a rubber plunger and a tip cap. The syringes are packed together with a sterile injection needle.

Pack size: 1 pre-filled syringe equipped with an automatic safety system to prevent needle stick injuries after use.
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Storage and shelf-life
Store at 2°C - 8°C (Refrigerate. Do not freeze). Keep the syringe in the outer carton. Product is for single use in one patient only. Contains no antimicrobial preservative. Discard any residue. Do not use after the expiry date on the carton.

Elonva can also be stored below 25^{o}C for up to 1 month. Do not use after this period.

POISON SCHEDULE OF THE DRUG

Schedule 4
Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

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DATE OF APPROVAL

21 July 2010

Therapeutic Goods Administration

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