

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Ovitrelle. This scientific discussion has been updated until 1 August 2004. For information on changes after this date please refer to module 8B.**

### 1. Introduction

Choriogonadotropin alfa is a recombinant version of the naturally occurring endogenous hCG. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary (CHO) cells that contain the gene coding for the  $\alpha$ - and the  $\beta$ -subunits of human chorionic gonadotrophin hormone. Choriogonadotropin alfa is isolated from the cell culture medium by conventional techniques applied to the purification of proteins. Ovitrelle is the first hCG preparation that is produced by recombinant techniques. Current hCG products contain hCG extracted from the urine of pregnant women. The production of hCG extracted from urine involves the collection and processing of large amounts of urine from post-menopausal women.

hCG is used to stimulate the final stage of ovarian follicular maturation and to provide hormonal support for the early corpus luteum in the treatment of female infertility. r-hCG is administered to trigger final follicular maturation and luteinisation after pharmacological stimulation of follicular growth.

One vial of Ovitrelle contains 285  $\mu$ g of choriogonadotropin alfa. The reconstituted solution contains 285  $\mu$ g per ml, claimed to ensure delivery of a 250  $\mu$ g dose. Ovitrelle is intended for subcutaneous injection. Ovitrelle is indicated in the treatment of:

- *Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF):* Ovitrelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth.
- *Anovulatory or oligo-ovulatory women:* Ovitrelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory patients after stimulation of follicular growth.

For both indications, the dose recommendation is one vial of Ovitrelle 250  $\mu$ g (equivalent to 6500 IU) to be administered 24 to 48 hours after optimal stimulation of follicular growth is achieved. The recommended dose for urinary preparations registered is one subcutaneous or intramuscular injection of maximally 10,000 IU at 24 to 48 hours after the last administration of hMG or FSH in assisted reproduction. The recommended dose in female sterility due to absence or infrequent ovulation is 5000-10,000 IU in 1-3 days following a treatment with hMG or FSH.

#### List of abbreviations

AEs	: adverse events
AUC	: area under the curve
B.P.	: British Pharmacopoeia
CHO	: chinese hamster ovary
ELISA	: enzyme-linked immunosorbent assay
EPDB	: extended population doubling banks
FBS	: foetal bovine serum
FSH	: follicle stimulating hormone
GMP	: Good Manufacturing Practice
GnRH	: gonadotrophin releasing hormone
hCG	: chorionic gonadotrophin
HH	: hypogonadotrophic hypogonadism
hMG	: human menopausal gonadotrophins
IM	: intravenous, muscular
IUI	: intrauterine insemination
IV	: intravenous
LH	: luteinising hormone
MCB	: master cell bank

OHSS	: ovarian hyperstimulation syndrome
r-hCG	: recombinant human chorionic gonadotrophin
RP-HPLC	: reversed phase high performance liquid chromatography
SC	: subcutaneous
SDS-PAGE	: sodium dodecyl sulphate polyacrylamide gel electrophoresis
SE-HPLC	: side exclusion high performance liquid chromatography
TSH	: thyroid stimulating hormone
u-hCG	: urinary human chorionic gonadotrophin
USP	: United States Pharmacopoeia
WCB	: working cell banks

## 2. Part II: Chemical, pharmaceutical and biological aspects

### *Composition*

Ovitrelle is a sterile and freeze-dried powder for solution for subcutaneous injection presented in glass vials with rubber stoppers. It is available in one dosage strength: 250 micrograms per vial of choriogonadotropin alfa (equivalent to a delivered dose of 6500 IU). The powder is to be reconstituted with the accompanying solvent (1.0 ml water for injections) presented either in ampoule or in vial. The finished product contains the following excipients: sucrose as a bulking agent, sodium hydroxide and phosphoric acid (concentrated), both as pH stabilisers. The pH of the reconstituted solution is 6.5-7.5. Nitrogen is used as an inert gas to fill the head space of the vial.

Except for the active substance, all the other components used in the composition of the medicinal product as well as the solvent comply with specific European Pharmacopoeia (Ph. Eur.) and/or United States Pharmacopoeia (USP) monographs. No human or animal derived components are used as excipients.

The primary container is a colourless glass vial sealed with a bromobutyl rubber stopper, aluminium seal ring and flip off cap. The stoppers are siliconised before use.

A ready to use liquid formulation in a pre-filled syringe was developed to facilitate administration of the product by the patient. Ovitrelle solution for injection in a pre-filled syringe contains 250 micrograms of choriogonadotropin alfa per 0.5 ml solution. The composition of the solution for injection dosage form differ from the powder in the excipients added to the thawed drug substance solution. Sucrose used as a bulking agent in the freeze-dried preparation is replaced by mannitol, while methionine and poloxamer 188 were selected as constituents for the liquid formulation due to their protective (towards oxidation) and stabilizing effect on the drug substance in solution. The primary container is a type I glass syringe with a halobutyl rubber plunger stopper and plastic plunger, and with a stainless needle.

### *Active substance*

The active substance of Ovitrelle is human chorionic gonadotrophin (r-hCG) produced in genetically engineered Chinese hamster ovary cells (CHO). Recombinant hCG is composed of two dissimilar non-covalently linked subunits, named alfa and beta. The  $\alpha$ -hCG subunit, common to all the gonadotropin hormones (FSH, TSH, LH, hCG), is 92 amino acid residues in length and the  $\beta$ -hCG subunit, which dictates the hormone specificity, is 145 amino acid residues in length.

The active substance has been extensively characterised using physico-chemical, biological and immunological assays. State-of-the-art analytical procedures have been used to elucidate the protein sequence and the oligosaccharide structures. For Comparison, the company has used hCG extracted from urine. Based on the data presented, the conclusion has been drawn that rhCG is comparable with the urine-derived species in terms of primary structure and glycosylation.

### *Development genetics and cell bank system*

The production process of choriogonadotropin alfa uses a transformed Chinese Hamster Ovary (CHO) host strain, which has been comprehensively described in the application. This strain was prepared by co-transfection into the genome of the parent CHO cell line of two genes of interest coding for the  $\alpha$ - and  $\beta$ -subunits. After transfection and selection, one subclone was chosen for further process development and was used to establish the Master Cell Bank (MCB). The methods used to establish

the MCB have been well described and involved standard techniques widely used in DNA recombinant technology.

Both expression constructs were used to co-transfect a Chinese Hamster Ovary (CHO) cell line. A detailed overview of the procedure was enclosed in the MAA. The procedure used for the amplification of the expression plasmids, cloning and selection procedures can be considered as a standard method and were sufficiently described.

The preparation as well as maintenance (location and storage conditions) of the Master Cell Bank (MCB) and Working Cell Banks (WCB) are described in detail in the documentation. Characterisation studies (phenotypic as well as genotypic testing) of the various cell banks were carried out using classical tests. All vials tested from each cell bank were found to be free of microbial contamination (bacteria/fungi and mycoplasma). In addition, viral safety has been well documented and is not a matter of concern. Genetic stability has been demonstrated.

### ***Fermentation and purification***

The fermentation process, from the cell culture inoculum expansion to the final cell harvest, has been adequately described in the application. The equipment and dedicated facilities as well as cleaning in place and sterilisation procedures are satisfactorily documented. The composition of the various culture media (including the origin of the various components) as well as the way to prepare the culture media used in the fermentation process have been thoroughly documented. The various relevant parameters recorded during each phase of the bioreactor cell culture process have been documented in detail. In-process controls assure appropriate cell growth and the absence of microbial contamination.

The downstream purification process leading to the r-hCG bulk solution has been described in detail. The purification procedure for r-hCG comprising a series of ultrafiltration units, chromatographic columns and viral nanofiltration unit is divided into five steps (step I to V). The chromatographic columns established represent a wide range of separation effects based on different physical principles. All starting materials used for the preparation of buffers and sanitisation solutions comply with the Ph. Eur. or are of analytical grade. Appropriate in-process controls performed after each purification step allow the monitoring of the performance of each step with respect to yield, purity, endotoxin, bioburden and pH. No reprocessing or reworking is envisaged throughout the entire purification process.

The production process of the active substance, which complies with Good Manufacturing Practice (GMP) requirements, has been adequately validated. Validation studies are documented in detail in the dossier. The various critical steps of the production process, from the cell culture to purification of choriogonadotropin alfa have been identified. Based on the results obtained regarding the upstream (cell culture) as well as the downstream (purification) processes, the capacity, robustness and reproducibility of the production process are satisfactory and lead to an active substance bulk solution with a reproducible good quality.

### ***Impurities***

As regards removal of impurities during the purification process, detailed investigations have been performed. Particular attention has been paid on process related impurities (residual DNA, host cell protein and culture medium protein, microbial/viral contamination, bacterial endotoxins), product related impurities (oxidation, dissociated subunits, aggregates) and contaminants (isopropyl alcohol, ammonium ion). In general, satisfactory in-process control results were reported. Potential microbiological and viral contamination is considered adequately controlled.

### ***Batch analysis, routine tests and specifications of the active substance***

Batch analysis results for six consecutive batches of active substance, representing those intended for marketing has been presented. According to the expert, batches have been included that were purified from early, mid and late harvests and between harvests from two different bioreactor runs. Batch results are consistent and conform to specifications.

The current analytical methods and specifications for the release of the active substance ensure consistent quality of the recombinant human luteinising hormone with respect to identity, purity, potency, and safety. An *in vivo* cell assay is being used to determine the hCG bioactivity of the active substance. The tests selected to be performed on a routine basis are satisfactory; their proposed limits are also considered as acceptable.

The various methods used for quality control of choriogonadotropin alfa have been described, justified, and validated for their analytical performances, and particularly in terms of accuracy, precision, limit of quantification, limit of detection, specificity, linearity/range and robustness. The proposed routine quality control test methods and specifications were selected in order to assess, on a routine basis, the identified key features.

Based on the physico-chemical and biological characterisation data provided, it can be concluded that sensitive and quantitative tests have been developed and validated for identity, purity, and potency of the active substance.

### ***Stability of active substance***

Long term stability testing was performed with four batches produced at manufacturing scale and stored at the recommended storage temperature. Supportive data are provided for several pilot scale batches. Based on the data submitted it is concluded that the proposed holding time of 24 months is sufficiently justified. A stability protocol has been provided for a test period of 60 months. The company committed to submit the results of this study on an ongoing basis to further justify the holding time.

### ***Other ingredients / Packaging material***

All excipients used to formulate the medicinal product are described in the European Pharmacopoeia monograph and are quality controlled accordingly. The immediate packaging of the powder for injection is a 3 ml vial made from colourless borosilicate type I glass (Ph. Eur.), which is covered with a W1816 bromobutyl rubber stopper (Ph. Eur.), protected by an aluminium seal ring and a flip off cap. The integrity of the container/closure system has been appropriately validated.

The solvent for reconstitution (sterile water for injections) is contained either in a 2 ml colourless vial with a siliconised bromobutyl rubber or in a 2 ml colourless glass ampoule.

The primary container of the solution for injection in a pre-filled syringe is a type I glass syringe with a halobutyl rubber plunger stopper and plastic plunger, and with a stainless needle.

### ***Product development and finished product***

Various formulations have been tested and the rationale for the formulation of Ovitrelle has been justified. Accelerated stability studies indicated that the product is most stable at pH 7, intermediate ionic strength and low di-electric constant. A freeze-dried preparation was selected because such a preparation can be stored at room temperature. No significant adsorption to the rubber closures or to syringes used to inject the reconstituted fluid was found. It is felt that the choice of the formulation has been sufficiently justified by the data provided. The company developed later on a ready to use solution for injection in a pre-filled syringe to facilitate administration of the product by the patient. This presentation requires storage in a refrigerator (2°C - 8°C). Within its shelf-life, the solution may be stored at or below 25°C for up to 30 days without being refrigerated again during this period.

### ***Method of preparation***

The standard batch size can range from 16,000 to 52,500 vials. The manufacturing process is straightforward and is typical for a protein parenteral product. The manufacturing process, which complies with Good Manufacturing Practice (GMP), has been described in sufficiently detail. It takes place in the manufacturing plant at Industria Farmaceutica Serono S.p.A., Bari, Italy or at Laboratoires Serono S.A. Aubonne, Switzerland. The manufacturing process has been adequately validated and is monitored using satisfactory in-process controls.

The manufacturing process of the water for injections, provided in vials or ampoules, is classical and has been described in detail. The manufacturing process, which complies with GMP, takes place at Hameln pharmaceuticals GmbH, Germany (for the ampoules) and Gensia Sicor Pharmaceuticals Inc., USA or Laboratoires Serono S.A., Switzerland (for the vials).

The solution for injection in a pre-filled syringe is manufactured and released at Industria Farmaceutica Serono S.p.A, Bari, Italy; packaging may also take place at Laboratoires Serono S.A. Aubonne, Coinsins, Switzerland.

For the validation of the manufacturing process, results on three batches of the finished product manufactured at the intended commercial scale have been provided. The data showed that the finished product consistently met the proposed specifications and demonstrated that the manufacturing process is consistently reproducible.

***Control tests and Specifications of the finished product***

The proposed tests and limits allow to check each batch of the finished product for identity, purity, safety, and potency. The same *in vivo* cell assay as for the active substance is being used to determine the hCG bioactivity of finished product. All test methods intended to be used for routine testing, have been validated for accuracy and reliability. Standard tests for sterile freeze-dried products (appearance, moisture content, cake weight, reconstitution time) and reconstituted product (degree of opalescence, degree of coloration, pH, particulate contamination, sterility, bacterial endotoxin) have been appropriately included in the specifications. The presented tests are considered appropriate to test the finished product for pharmaceutical characteristics, identity, purity and r-hCG concentration.

In general, the proposed specifications are acceptable and, although some limits should be tightened, the limits are reasonable and based on the experience already gained. The company committed to tighten some of the limits of the specifications of the finished product.

### ***Stability of the finished product***

The shelf-life of the product is 24 months at  $25 \pm 2^\circ\text{C}$  and protected from light. Real time, real temperature stability data have been generated for nine batches produced at pilot scale during different stages of development. Three batches of finished product produced at full manufacturing scale in the final manufacturing site are also included in the stability program. For those batches, only six or, for some parameters, nine months results were initially available. Therefore the assessment of the stability of the finished product is mainly based on the results obtained with the pilot scale batches. Updated results up to 36 months have been submitted on an on-going basis as follow-up measures.

The shelf-life of the solution for injection dosage form is 2 years in a refrigerator. The pre-filled syringe may be stored by the patient at or below  $25^\circ\text{C}$  for up to 30 days without being refrigerated again during this period. Interim results at 18 months on 3 batches manufactured at Industria Farmaceutica Serono S.p.A. have been provided. All results complied with the approved specifications. The stability studies are continuing in accordance to the protocol.

### ***Viral safety***

The Master Cell Bank (MCB), Working Cell Bank (WCB) and the Extended Population Doubling Bank (EPDB) have been closely examined for contamination with viral agents. Using a battery of *in vitro* and *in vivo* tests no endogenous or adventitious viruses were detected and therefore, the tested cell lines exhibit a satisfactory level of viral safety. It can be concluded that cell banks were validated in accordance with the CPMP/ICH note for guidance on quality of biotechnological products and can be used as safely as possible as cell substrate for r-hCG production.

Choriogonadotropin alfa is manufactured using a serum free cell culture process. However, a small amount of Foetal Bovine Serum (FBS, which is of bovine origin), is used in the inoculation phase of the manufacturing process.

FBS was derived from animals sourced in USA and Canada, which are BSE-free countries, and has been prepared in accordance with the "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (CPMP/BWP/1230/98). A representative certificate of suitability from each FBS supplier was submitted and the Company committed to audit the supplier/manufacturer of FBS at regular intervals.

Besides FBS, the manufacturing process of choriogonadotropin alfa involves the use of trypsin, which is of porcine origin. It is certified to be porcine parvovirus free, to comply with 9 CFR 113.53, and that its production involves an extended extraction at acid pH. The viral safety with regard to trypsin is therefore considered to be sufficiently ensured.

The purification process has been appropriately validated and the capacity of the production process to remove/inactivate viruses has been adequately demonstrated.

Overall, the viral safety of choriogonadotropin alfa is assured by, i) the satisfactory viral testing of cell banks, biological reagents, and unprocessed bulk, ii) the robustness of the production process and iii) the satisfactory cumulative reduction factors achieved by the purification process. The production process is effective to clear potential viruses that could be present in the unpurified product.

### ***Discussion on the chemical, pharmaceutical and biological aspects***

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with the requirements in the Note for Guidance on Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology as well as other relevant guidelines. The information provided in the application demonstrated consistent production of choriogonadotropin alfa achieving a well-defined quality for the active substance and the finished product as well as for the solvent for reconstitution. The fermentation and purification of the active substance are adequately controlled. Choriogonadotropin alfa has been well characterised using state-of-the-art methods with regard to its physicochemical characteristics. The manufacturing process of the finished product, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail and product specifications are adequate. In general, methods to control the quality of the product are adequate. Moreover, this is a product of biological origin for which all the virological aspects have been satisfactorily addressed. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of

transmitting animal spongiform encephalopathy agents via medicinal products. Stability data support a shelf-life of 24 months for the finished product.

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Ovitrelle is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

## **2. Part III: Toxicopharmacological aspects**

The active substance of Ovitrelle, choriogonadotropin alfa (recombinant human chorionic gonadotrophin, r-hCG), is structurally similar to human chorionic gonadotrophin (hCG). hCG is a glycoprotein normally produced by trophoblast cells as early as 6 days post-conception, which helps to maintain and stimulate the corpus luteum and early placento-foetal endocrine function. In normal pregnancy its production by the early trophoblast and subsequently by the organised placenta is essential for maintenance of the early stages of pregnancy. Activation of the LH/hCG receptor regulates steroidogenesis in the ovary by theca and granulosa cells, and by Leydig cells in the testis; it affects the essential early stage of mitochondrial conversion of cholesterol to pregnenolone. The identity of the actions of hLH and hCG has been exploited therapeutically by using various preparations of hCG, notably u-hCG extracted from the urine of pregnant women, to mimic the normal late surge in LH secretion. This results in maturation of oocytes, follicular rupture and formation of normal hormonal secretion by the corpus luteum.

### ***Pharmacodynamics***

Investigations aimed to demonstrate identical pharmacological characteristics of r-hCG and u-hCG. The *in vivo* and *in vitro* experiments have shown that:

- r-hCG has the same binding affinity to the LH/hCG receptor as u-hCG,
- it stimulates progesterone production by MA-10 cells with the same potency as u-hCG and several national and international reference standards,
- it had the same potency as several reference standards and u-hCG in Ph. Eur. and USP bioassays in the rat, and,
- in a detailed test in the primed adult female rhesus monkey, r-hCG and u-hCG stimulated the production of oocytes of the same maturity, and exerted the same hormonal activities on luteinisation of ovarian follicles.
- The time course of the actions of r-hCG and u-hCG were identical in the *in vivo* studies.

Taken together, r-hCG induces ovulation and produces oocytes of sufficient maturity to be capable of being fertilized.

No significant or consistent action of hCG (200 to 20,000 IU/kg) on blood pressure, heart rate, several measures of left ventricular function, ECG or respiration in anaesthetised rats and dogs have been observed. Interaction studies were not performed.

### ***Pharmacokinetics***

The available information on pharmacokinetics in laboratory animals was limited. Pharmacokinetics were only extensively investigated in monkeys after single dose and repeated dose administration. Bioavailability of r-hCG in cynomolgus monkeys was high after single intramuscular (100%) and subcutaneous (85%) administration. Terminal half-life was in the range 20 – 30 hours. Distribution volume at steady state was about 0.1 – 0.2 l/kg after intravenous administration, 0.3 l/kg after intramuscular administration and 0.5 l/kg after subcutaneous administration. After single subcutaneous administration T<sub>max</sub> was about 6 hrs. After intravenous administration the pharmacokinetic parameters of u-hCG and c-hCG in monkeys were similar. The kinetics of r-hCG, after single IV injection at 20, 100 and 500 IU/kg was dose linear. The repeated dose study, where r-hCG 100 IU/kg SC was injected daily for 7 days, showed that the AUC (d<sub>7</sub>)/AUC (d<sub>1</sub>) ratio ranged from 1.1-1.5 (1.3 ± 0.2) indicating the possibility of a slight accumulation of r-hCG.

The steady state was attained after the third dose, i.e. within 72 hours after the first administration, which is in agreement with the calculated elimination half-life of about  $23.7 \pm 2.5$  hours. Exposure in the toxicity studies increased more or less linearly with dose.

Repeated administration in monkeys and rats induced formation of neutralising antibodies, in some animals this resulted in accelerated elimination of the compound and decrease (down to zero) of circulating concentrations in the course of the toxicity experiments.

Toxicokinetic data in monkeys and rats showed that in the toxicity experiments exposure was high enough (at the maximum examined doses systemic exposure was more than 50 times the expected human exposure).

No specific pre-clinical distribution, metabolism and elimination studies were performed. However, considering the nature of the molecule, further information on pharmacokinetics in laboratory animals is not deemed necessary.

In conclusion, there is sufficient information available to understand the kinetics of r-hCG in animals and to show its comparability in the monkey to that in man, that its kinetics is simple, that slight accumulation may occur on daily dosing to reach steady state after 3 days, that the bioavailability of a SC or IM dose is high, and that it is indistinguishable from the established u-hCG.

### ***Toxicology***

A limited toxicological testing programme was conducted which albeit met the regulatory requirements with respect to the intended use only once or on a few occasions in the life of a non-pregnant young woman. Due to the uniquely high specific content of the r-hCG preparations, very large doses could be employed in toxicological studies.

The maximum dose in humans could be estimated to correspond to approximately 200 IU/kg/day in monkeys and rats when administered subcutaneously.

All the studies conformed to GLP (Good Laboratory Practice).

### ***Single dose toxicity***

Acute toxicity studies were conducted with r-hCG in rats and cynomolgus monkeys treated by IV and SC routes. r-hCG had almost no effect in the single dose studies apart from the anticipated slight reduction in testicular weight and increase in ovarian weight, associated with pharmacological changes in spermatogenesis and in the appearance of a number of corpora lutea and ovarian follicles. The highest dose level tested of 200,000 IU/kg represents a 1000-fold multiple of the human dose (up to 200 IU/kg/day).

### ***Repeated dose toxicity***

The repeated dose toxicity was tested in male and female rats and Cynomolgus monkeys receiving up to 20,000 IU/kg/day for 4-weeks of r-hCG by intravenous or subcutaneous injection. Additionally, r-hCG was tested up to 5,000 IU/kg/day in a 26 weeks SC study in male Cynomolgus monkeys. In the latter study u-hCG (500 IU/kg/day) was used as a comparator.

In rats, there was no severe toxic action but there were many features of induced hormonal disturbances attributed to the known actions of hCGs in any responsive species. They included enlargement of the seminal vesicles and prostate and smaller testes, associated with degeneration of germinal epithelium and hyperplasia of interstitial cells, enlargement of the ovaries with many corpora lutea, and hyperplasia of the vaginal mucosa. These actions were considered to be due to the LH-like action of hCG in the rodent as well as to the stimulation of steroid levels, that also caused some haemodilution, hepatocellular hypertrophy and thymus atrophy. The effects largely disappeared during the recovery period. Serum antibodies to r-hCG developed in about half of the animals in the IV study, and virtually all animals in the SC study, which in individual rats resulted in an apparently very low level of circulating r-hCG in the latter half of the experiment. As expected, plasma oestradiol and testosterone levels were very high.

In monkeys, the treatments were well tolerated and no toxic actions were found. The top- and mid-dose males showed increased rate of weight gain. In the males there was interstitial cell hyperplasia in



the testes and secondary effects in the prostate. Females showed an increased number of corpora lutea. There were corresponding changes in serum testosterone (increased) in males. No changes in oestradiol were noted in females. There was slight inflammatory cell infiltration at the injection sites. In the IV study, antibodies to r-hCG were found in all top-dose animals, all mid-dose males and in a few mid-dose females, and serum levels of r-hCG were maintained but did tend to fall in those animals with antibodies. In the SC study, antibody formation occurred in all dose groups and the titre was dose-related. The pathological effects lessened during the 4-week recovery period. In the 26-weeks test, there was an increased rate of weight gain and enlargement of the testes and seminal vesicles and histologically appreciable hyperplasia of mammary acinar epithelium. Enlargement and hypercellularity of the anterior pituitary was also noted. All these actions were attributed to the effects of increased production of testosterone due to the well known pharmacological actions of r-hCG or u-hCG. The production, morphology and functionality of sperm were normal.

### ***Reproductive toxicity***

Reproduction studies were not performed. Given the nature of the active substance and the therapeutic indication, reproductive studies in female test animals are not required. r-hCG is intended for the treatment of infertile women, who are most unlikely to be pregnant. r-hCG is substantially identical to the native human molecule, and the well known u-hCG has been extensively administered to humans for many years under clinical circumstances. In rats, r-hCG is abortifacient and can affect fetal survival and growth.

### ***Mutagenic potential***

Four mutagenicity studies were submitted, although according to the recommendations of ICH3 studies to the mutagenic potential are not necessary. r-hCG was negative in well performed *in vitro* gene mutation tests in bacteria (Ames test) and mammalian cells (HGPRT test in V79 cells), in an *in vitro* chromosome aberration test with human lymphocytes, and an *in vivo* mouse bone marrow micronucleus test. These studies demonstrated that r-hCG is not a potential mutagen.

### ***Oncogenic/carcinogenic potential***

No studies were conducted. Since the intended clinical use is a single dose on a few occasions, since no genotoxicity was detected, and no other observations have given rise for a special concern, it is considered that there is no need for testing for carcinogenic potential of Ovitrelle.

### ***Local tolerance***

In a local tolerance study, conducted in New Zealand rabbits using a single intramuscular injection, half of the clinical volume (same concentration) did not cause local irritation. However, r-hCG is intended to be used by subcutaneous route. Skin sensitisation was not tested and a justification was not provided.

In repeated dose studies in rats and monkeys no reactions at the injection sites were clinically observed after subcutaneous and intravenous administration. Slight perivascular mononuclear cell cuffing was observed in some animals, indicative for a delayed hypersensitivity reaction. Clinical experience do not give indications for hypersensitivity reactions. The Company does not justify the absence of a local tolerance study with subcutaneous administration and a skin sensitisation study, but based on the results of the repeated dose studies it is concluded that subcutaneous administration of r-hCG does not induce irritation, but hypersensitivity might occur.

### ***Impurities, excipients and degradation products***

Due to the use of the same purification process the impurity levels in the drug substance were very consistent over the development process. The batches were monitored for DNA, serum derived proteins, oxidised forms, free subunits as well as fragments and aggregates in routine testing. All results were well within the preliminary specification.

### ***Environmental risk assessment***

Both r-hCG and native hCG are simple glycoproteins and will be readily catabolised by organisms throughout the environment. There is no foreseeable environmental risk associated with the use of r-hCG.

### **Discussion on toxico-pharmacological aspects**

Recombinant human chorionic gonadotropin, r-hCG, induces ovulation and produces oocytes of sufficient maturity to be capable of being fertilized.

The available information on pharmacokinetics and toxicokinetics in laboratory animals was limited. Pharmacokinetics was only extensively investigated in monkeys. Distribution, metabolism and excretion were not examined. However, considering the nature of the molecule, further information on pharmacokinetics in laboratory animals is not deemed necessary.

Based on the available preclinical information there is no concern about the safety for patients receiving a single subcutaneous administration of 500 µg r-hCG.

Repeated dose toxicity studies in monkeys and rats have shown only the anticipated endocrine effects of high doses of this gonadotrophin, including some of the known oestrogenic actions in the rat. Antibodies were formed after a few weeks both in the rat and monkey, which greatly accelerated clearance of the injected r-hCG but did not completely reverse the endocrine actions during continued dosing. The effects all disappeared completely, or almost, during the 4-week recovery period. There was a slight inflammatory reaction at the injection sites.

Reproductive toxicity studies were not performed. Given the nature of the drug and the therapeutic indication, the performance of reproductive studies in female test animals is not necessary. The substance was not genotoxic. Local tolerance problems, in the form of irritation at the injection site, is not an issue. Hypersensitivity is not expected based on clinical experience.

Overall, pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of choriogonadotropin alfa to induce ovulation. Results from the toxicology programme did not raise particular concerns for the safe use of choriogonadotropin alfa.

## **4. Part IV: Clinical aspects**

### **Clinical pharmacology**

#### ***Pharmacodynamics***

Pharmacodynamic properties of recombinant hCG (r-hCG) administered at a dose of 2,500 IU (125 µg) by three different routes [intravenous (IV), intramuscular (IM), and subcutaneous (SC)] were evaluated in 12 healthy volunteers (6 men and 6 women) (GF 7013). The 6 male volunteers were previously pituitary down-regulated (testosterone  $\leq 1.5 \text{ nmol.l}^{-1}$  and LH  $\leq 2.5 \text{ IU.L}^{-1}$ ) with a subcutaneous (SC) injection of a depot preparation of a GnRH-agonist (Zoladex® 3.6 mg) and the 6 female volunteers used an oral contraceptive for ovarian suppression. Pharmacodynamics of r-hCG were determined by measuring testosterone (T), luteinising hormone (LH), estradiol (E<sub>2</sub>), and inhibin in males and by measuring androstenedione in females during repeated dosing. The various markers were analysed as a function of time.

The chosen pharmacodynamic evaluations indicate that exogenous administration of r-hCG 250 µg after pituitary/ovarian down-regulation is capable of initiating the aimed effect of stimulation of the testes/ovaries, as shown by the increase in testosterone, inhibin and estradiol in male volunteers and increase in androstenedione and testosterone in female volunteers. The obtained effects are comparable with those observed with the reference product Profasi 5,000 IU.

#### ***Pharmacokinetics***

Clinical pharmacokinetics were adequately investigated in four phase I studies and a population pharmacokinetic study. After a 5,000 IU SC administration, Profasi (u-hCG) and Ovitrelle (r-hCG) were bioequivalent on AUC and C<sub>max</sub>. Absolute bioavailability is about 40%. There are no indications that r-hCG is metabolised differently than endogenous hCG. Pharmacokinetic parameters in patients, obtained by population pharmacokinetic analysis, are in range with those seen in the healthy volunteers. A correlation was observed between V/F and BMI, resulting in a 20% difference in predicted drug exposure between treatments with u-hCG and r-hCG. Further discussion on the consequences of this correlation is necessary. Pharmacokinetic interaction studies and studies in special patient groups are not necessary.

considering the indication, the dosing scheme of a single dose, and the metabolic/excretion profile of r-hCG.

Pharmacokinetic/pharmacodynamic analysis showed that a delay was present between the hCG concentration profile and the pharmacodynamic response. Maximum hCG levels are observed 12 h after SC injection, while the maximum testosterone and androstenedione effect appears to occur at around day 3. From graphical presentation it can be concluded that the pharmacodynamic effects produced by both r-hCG and u-hCG were similar and this further supports the pharmacokinetic bioequivalence.

A liquid formulation was used in early clinical trials. Bioequivalence between the liquid and the freeze-dried formulation has been demonstrated in a human pharmacology trial.

### ***Clinical Experience***

The clinical documentation consists of 8 clinical studies, of which 5 are related to the indications requested. All studies were conducted according Good Clinical Practice (GLP). Signed audit certificates are present in the dossier. An overview of all studies is given in table 1. Table 2 summarises the design, key efficacy, and secondary efficacy and safety endpoints for the three clinical studies: GF 7648, GF 7927 and GF 9073. Table 3 summarises the objectives of these studies.

**Table 1 : clinical efficacy studies**

Report n°	- Design - Status	Number* subjects with and sex	of age	Diagnosis Duration of treatment	Test product Dosage regimen Route of administration
<b>Placebo Controlled Studies</b>					
GF 8936	DB, randomized, multicenter, parallel group, dose-finding <b>Ongoing</b>	39, ≥ 18*, male		HIV-related hypogonado- trophic hypogonadism  3 months	r-hCG, 125 µg, SC, BIW r-hCG, 250 µg, SC, BIW r-hCG, 500 µg, SC, BIW Placebo, SC, BIW
GF 9250	DB, randomized, multicenter, parallel group <b>Ongoing</b>	26* 47-90 female		Breast cancer 2 weeks	r-hCG, 500 µg, IM, TIW Placebo, IM, TIW
<b>Controlled Studies with Reference Therapies</b>					
GF 7648	DB, double-dummy, randomised, multicenter, parallel group Phase III <b>Completed</b>	190**, 20-35, female		Infertility with regular ovulatory menstrual cycles single dose	r-hCG 250 µg, SC u-hCG 5000 IU, SC
GF 7927	OL, randomised, comparative, multicenter, parallel group, Phase III <b>Completed</b>	275**, 18-38, female		Infertility with regular, spontaneous ovulatory menstrual cycles single dose	r-hCG, 250 µg, SC r-hCG, 500 µg, SC u-hCG, 10000 U, IM
GF 8209	DB, double-dummy, randomised, comparative, multicenter, parallel group, Phase III <b>Completed</b>	234, 20-39, female		Infertility due to ovulatory dysfunction single dose	r-hCG, 250 µg, SC u-hCG, 5000 IU, SC
GF 9073	DB, double-dummy, randomised, comparative, multicenter, parallel group, Phase III <b>Completed</b>	84**, 20-38, female		Infertility with regular spontaneous ovulatory menstrual cycles	r-hCG, 250 µg, SC u-hCG, 5000 IU, IM Single dose
GF 9779	OL, randomised, comparative, parallel group <b>Completed</b>	7* 29-39, female		Infertility due to tubal disease, male factor	u-hCG, 5000 IU, IM r-hCG, 250 µg, SC Single dose
<b>Non-controlled Studies</b>					
IMP 20570	OL <b>Ongoing</b>	8 bone age >13 male		Hypogonado- trophic hypogonadism	r-hCG, 100 µg, SC, BIW FSH, 75-225 IU, SC, TIW, per response

\*Patient numbers for ongoing protocols were taken from the protocol; \*\*No. of patients treated with hCG, TIW: thrice weekly; BIW: twice weekly, TIW: thrice weekly

**Table 2: Design, key efficacy and safety endpoints of GF 7648, GF 7927, GF 9073**

	<b>Study GF 7648</b>	<b>Study GF 7927</b>	<b>Study GF 9073</b>
<b>Study Title</b>	A Phase III, double-blind, double-dummy, randomised, multicentre study to compare the safety and efficacy of r-hCG SC with that of u-hCG (Profasi SC), for inducing final follicular maturation and early luteinisation in women undergoing superovulation with recombinant human FSH (Gonal-F®) prior to IVF/ET	A phase III, open, comparative, randomised, multicentre study to compare the safety and efficacy of r-hCG SC, with that of u-hCG (Profasi IM), for inducing final follicular maturation and early luteinisation in women undergoing superovulation with highly-purified FSH (Metrodin XP™) prior to IVF/ET	A Phase III, double-blind, double-dummy, randomised, multicentre study to compare the safety and efficacy of r-hCG with that of u-hCG (Profasi IM) for inducing final follicular maturation and early luteinisation in women undergoing superovulation with recombinant human FSH (Gonal-F) prior to IVF/ET and ICSI/ET
<b>No. of Centres</b>	9	20	2
<b>Countries</b>	France, Germany, The Netherlands, Sweden, Italy, UK, Israel	USA	Australia, New Zealand
<b>No. of Subjects Planned</b>	200	300	80
<b>No of Subjects Treated with FSH</b>	205	296	90
<b>No. of Subjects Treated with hCG</b>	190	275	84
<b>Design</b>	Randomised, double-blind, double-dummy	Randomised, open, comparative	Randomised, double-blind, double-dummy

**Table 3: Objectives of studies GF 7648, GF 7927 and GF 9073**

	Study GF 7648	Study GF 7927	Study GF 9073
<b>Efficacy</b>	<ul style="list-style-type: none"> <li>To determine equivalence on the number of oocytes retrieved per patient between the patient groups treated with 250 µg r-hCG SC and Profasi 5 000 IU SC.</li> <li>Secondary end points: No. of oocytes retrieved No. of mature oocytes 2 PN fertilised oocytes No. of 2PN or cleaved embryos Implantation rate per ET Mid-luteal endometrial thickness Overall pregnancy rate Clinical pregnancy rate Serum Progesterone Serum hCG</li> </ul>	<ul style="list-style-type: none"> <li>To determine equivalence on the number oocytes retrieved per patient between the patient groups treated with 500 µg r-hCG SC and Profasi 10 000 U USP IM.</li> <li>To determine equivalence in the primary endpoint between the two doses of r-hCG, 250 and 500 µg.</li> <li>Secondary end points similar to those of study 7648</li> </ul>	<ul style="list-style-type: none"> <li>To determine equivalence on the number oocytes retrieved per patient between the patient groups treated with 250 µg r-hCG SC and Profasi 5 000 IU SC.</li> <li>Secondary end points: No. of oocytes retrieved No. of mature oocytes No of 2PN fertilised oocytes No. of 2PN or cleaved embryos Implantation rate per ET Overall pregnancy rate Clinical pregnancy rate Serum progesterone Serum hCG</li> </ul>
<b>Safety</b>	<ul style="list-style-type: none"> <li>To determine the safety and local tolerance of r-hCG, 250 µg, administered SC.</li> </ul>	<ul style="list-style-type: none"> <li>To determine the safety and local tolerance of r-hCG 250 µg and 500 µg administered SC.</li> </ul>	<ul style="list-style-type: none"> <li>To determine the safety and local tolerance of r-hCG, 250 µg, administered SC.</li> </ul>

The major difference between the clinical studies is that the US study was conducted as an open-label study, whereas the other two studies engaged a double-blind, double-dummy design. The choice of an open design was due to the fact that in Australia and the USA Profasi is indicated for IM administration only, whereas in Europe and Israel Profasi is indicated for IM and SC injection. Because Ovitrelle is to be administered SC, blinding of the US study would have required an SC placebo for Ovitrelle and an IM placebo for Profasi. This would have been a significant logistical problem, as the Company does not manufacture Profasi in the US. As a protection against the potential bias inherent to an open-label study, patients were not to be randomised until the day of hCG administration, after adequate follicular development was documented. In the other studies, patients were randomised at the start of FSH treatment, after confirmation of down-regulation. Additionally, the US study included third treatment arms, 500 µg Ovitrelle, 10,000 IU Profasi (the standard dose used in the US), and 250 µg Ovitrelle, to include the dose-range currently approved in the USA.

#### *Major inclusion criteria*

1. Infertility defined as a woman desiring a pregnancy and having failed to conceive after at least 2 years of unprotected coitus. The couple's infertility could attributable to any of the following causes: tubal factor, mild endometriosis (American Fertility Society classification I-II), unexplained causes (in this case infertility had to be at least 3 years. Amendment I allowed severe male factor as an additional cause of infertility, but only if ICSI was to be performed in this study)
2. A male partner with semen analysis within 6 the past months showing acceptable values of semen
3. Age of 20-38 years
4. Regular spontaneous ovulatory menstrual cycles of 25-35 days
5. During follicular phase (day 2-4) serum levels were to be in the following range: FSH ≤ 12 IU/l, LH ≤ 13.5 IU/l, prolactin (PRL) ≤ 800 mIU/l, T ≤ 3.5 nmol/l

6. Presence of both ovaries
7. No more than 3 previous assisted conception cycles.

#### *Major exclusion criteria*

1. Clinical significant systemic disease (e.g. insulin-dependent diabetes, epilepsy, severe migraine, intermittent porphyria, hepatic, renal or cardiovascular disease, severe corticoid-dependent asthma)
2. Polycystic ovarian syndrome (PCOS)
3. Previous history of severe ovarian hyperstimulation syndrome (OHSS)
4. Previous IVF or GIFT failure due to either sperm fertilisation, or poor response to gonadotrophin therapy (poor responders) Poor responders were defined as women who matured  $\leq 2$  follicles in a previous attempt.

#### *Treatment scheme*

The general treatment plan was similar in all studies. Once eligibility was established, patients were pituitary down-regulated with a gonadotrophin releasing hormone agonist (GnRH-agonists leuprolide acetate or nafarelin). When down-regulation was confirmed by  $E_2$  determination, patients underwent ovarian stimulation with FSH. In studies 7648 and 9073, Gonal-F (= r-hFSH) was used, whereas in the US study MetrodinXP (= purified u-hFSH) was used since Gonal-F was not registered in the USA at the time of study initiation. FSH starting dose was in accordance with each centre's normal practice in two of the three studies. When a dominant follicle of  $\geq 18$  mm with at least two other follicles of  $\geq 16$  mm was present and the level of  $E_2$  was deemed acceptable for the number of follicles present (around 150 pg/follicle), hCG was administered. Oocytes were retrieved 34-38 hours after hCG injection and fertilised *in vitro*. No more than 3 embryos were replaced. A dose of 200 mg/day of progesterone by the vaginal route was used for luteal phase support from the day of ovum pick up (OPU) for at least two weeks or until menstruation occurred. Patients were allowed to participate in one cycle only per study.

#### *Clinical efficacy*

The number of oocytes retrieved was considered the primary parameter in all three studies. Secondary efficacy parameters included, among others, oocyte maturity and quality, fertilisation, implantation and pregnancy. In previous studies using u-hCG in similar patients, the mean number of oocytes retrieved was 9.0 with a standard deviation of 5.0. It was assumed that to demonstrate equivalence with a probability of 95% and 97.5%, respectively, that the limits of the 90% CI of the difference ( $\Delta$ ) in the mean number of oocytes retrieved between the u-hCG and r-hCG treatment groups would be within the acceptable clinically relevant range of  $\pm 3$  oocytes.

Given that subjects who withdraw or drop out of the treatment group or the comparator group will tend to have a lack of response and, hence, the results using the full analysis set may be biased toward demonstrating equivalence, the main analyses were based on evaluable patients. Analyses based on all patients were considered supportive analyses and the results of both analyses were to be compared (study GF 7648). In study GF 7648, 172 evaluable patients (86 per group) were required to demonstrate equivalence with a probability of 97.5%. Based on earlier study results, it was assumed that 20% of patients might be non-evaluable, so a total number of 200 patients was randomised. In study GF 7927, it was determined that 300 patients would be required to demonstrate equivalence with a probability of 95% between treatment groups (Ovitrelle 250 versus Ovitrelle 500 and Ovitrelle 500 versus Profasi 10000). Study GF 9073 was conducted to provide supporting data for the larger multicentre studies that were powered to show equivalence of Profasi and Ovitrelle. With the sample size of this study, the power to declare the two treatments equivalent, according the assumption made in both pivotal studies, was about 68%.

#### *Results and conclusion on efficacy*

The primary efficacy endpoint was the same in all three studies: the number of oocytes retrieved per patient at ovum pick-up (OPU). The mean number of oocytes was similar across the hCG treatment groups within each study. Results of the statistical testing chosen as discussed in the several study protocols indicated equivalence according to the predefined delta. In all studies, indifferent from the

data set used for analysis, the limits of the 90% CI's fell within the acceptable clinically relevant range of  $\pm 3$  oocytes.

A large number of secondary endpoints were analysed in all three studies. No statistically significant differences regarding secondary efficacy parameters were observed between Ovitrelle 250 µg and Profasi 5000 IU, except for 2PN fertilised embryo's. Additionally, in the US-study, a statistically significant higher number of 2 PN fertilised oocytes was observed in the 500 µg Ovitrelle group in comparison with the 250 µg group.

#### *Women undergoing superovulation prior to assisted reproduction techniques such as IVF*

The aim of both pivotal studies was to demonstrate equivalence between a single dose of Ovitrelle 250 µg and Profasi 5000 IU in one study and Profasi 10,000 IU in a second study in this indication with a probability of 95% and 97.5%, respectively, that the limits of the 90% CI of the difference ( $\Delta$ ) in the mean number of oocytes retrieved between the u-hCG and r-hCG treatment groups would be within the range of  $\pm 3$ . This difference of up to 3 oocytes as the clinically relevant range in both equivalence studies can be considered clinically acceptable. As this aim of equivalence between Ovitrelle 250 µg and Profasi 5000 IU was reached in one study and between Ovitrelle 250 µg and Profasi 10,000 IU in a second study, it is concluded that the efficacy of Ovitrelle 250 µg in this indication is sufficiently proven by the clinical documentation presented. This conclusion is additionally supported by the outcome on secondary efficacy parameters in which, except for serum hCG in one of the studies, no significant differences between treatment groups were noted.

Clinical data obtained in the US study, that investigated the clinical performance of both 250 µg and the 500 µg of Ovitrelle, indicated no significant dose-dependent effects regarding the primary efficacy parameter. Except for 2PN fertilised embryo's and mid-luteal progesterone serum levels, no statistically significant differences were noted between 250 µg and 500 µg regarding secondary efficacy parameters tested. The presented clinical data do not demonstrate that these differences can lead to a clinically relevant additional efficacy with this higher dose in comparison with the 250 µg dose that supports approval of 500 µg dose of Ovitrelle. Furthermore, this conclusion is supported by the outcome on the second primary efficacy parameter in this study, determination of equivalence between Ovitrelle 250 µg and Ovitrelle 500 µg, which according to the predefined delta in the study plan ( $\pm 3$  oocytes), was achieved. Therefore the Company dropped their initially proposed dose recommendation of one or two vials of Ovitrelle (250 µg or 500 µg) to be administered 24 to 48 hours after optimal stimulation of follicular growth is achieved. At present, only the administration of a dose of one vial Ovitrelle (250 µg) is recommended.

#### *Anovulatory or oligo-ovulatory women*

No data on Ovitrelle regarding this indication was available in the initial application and one study which investigating the efficacy and safety of Ovitrelle 250 µg versus Profasi 5000 IU in this indication was ongoing at the time of submission. Following CPMP's objection to this indication, the Company completed a non-inferiority trial in the indication of anovulatory or oligo-ovulatory women, (Study GF 8209). This study was a double-blind, double-dummy, randomised, multicentre study to compare the safety and efficacy of recombinant human Chorionic Gonadotrophin (Ovitrelle) with that of urinary human Chorionic Gonadotrophin (Profasi) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F). In this study a dose of 250 µg of r-hCG was compared to 5000 IU u-hCG. Clinical non-inferiority was pre-specified as the difference in the proportions of the patients who achieved ovulation in the u-hCG and r-hCG treatments should not be lower than -20% in favour of u-hCG. The argumentation for the delta chosen was that in previous studies using u-hCG after stimulation with r-hCG in similar patients, the proportion of patients who achieved ovulation after receiving hCG was about 80%. This clinically relevant range in this non-inferiority trial can be considered clinically acceptable also in view of the outcome, although the provided justification of the delta chosen is only minimally as any reference is absent.

Efficacy of r-hCG (Ovitrelle) was demonstrated to be non-inferior to that of r-hCG with regard to the primary efficacy endpoint of ovulation, defined by mid luteal phase serum progesterone 30 nmol/l or clinical pregnancy whether or not mid-luteal P<sub>4</sub> was  $\geq 30$  mmol/l. The proportion of patients who



ovulated (analysis performed on all patients data set) was 91.9% for the r-hCG group and 85.9% in the u-hCG group. The lower limit of the one-sided 95% confidence interval for the treatment effect is – 3.7%, which is above the predefined limit of –20%. The secondary efficacy parameters regarding pregnancy showed no statistically significant differences between groups.

It is concluded that the currently submitted data in support of the indication of anovulatory or oligo-ovulatory women are considered sufficient clinical evidence to grant this indication for the 250 µg dose of Ovitrelle.

## Clinical safety

### *Safety parameters*

Safety assessments were focused on monitoring of adverse events, including OHSS, and assessment of local reactions to r-hCG and u-hCG injections by using a patient diary card. Safety laboratory evaluations and measurements of antibodies to the study drugs were performed before and after treatment.

A post-treatment visit including general physical examination, routine haematology, clinical chemistry and urinalysis testing, and blood sampling for assessment of potential antibodies to the study drug would occur 15 to 17 days following administration of hCG.

### *Patient exposure*

As of March 31, 1999, the data cut-off date for this marketing authorisation application, the clinical file of Ovitrelle included data on 535 patients. The overall extent of exposure to Ovitrelle by gender and by indication for which safety data are available is summarised in the following table.

**Table: Number of patients exposed to individual dosage regimens of Ovitrelle by indication and gender**

Total dose/subject	Indication	Female	Male	Total
250 µg (1x) SC	Female infertility	334	0	334
500 µg (2x 250)	Phase I	12	12	24
500 µg (1x) SC	Female infertility	89	0	89
1,000 µg (3x 125 SC, IM, IV + 5x 125 SC)	Phase I	6	6	12
1,200 µg (2x 100/week, 6 weeks SC)	Male Hypo**	0	8	8
1,275 µg (25, 250, 1,000 IV)	Phase I	6	6	12
2,200 µg (1x) IV	Phase I	6	0	6
< 3,000 µg (2x 125/week for 12 weeks SC)	HIV-hypogonadism	0	10	10
< 3,500 µg (2x 500/day for 14 days SC)	Breast cancer	21	0	21
< 6,000 µg (2x 250/week for 12 weeks SC)	HIV-hypogonadism	0	10	10
< 12,000 µg (2x 500/week for 12 weeks SC)	HIV-hypogonadism	0	9	9
<b>TOTAL</b>		<b>474</b>	<b>61</b>	<b>535</b>

\*Categories of “total dose/subject” are mutually exclusive., \*\*: hypogonadotrophic hypogonadism

## Adverse events and serious adverse events (AEs)

*Pharmacology studies (Phase I no. GF 7012, GF 7013, GF 7014, GF 8927)*

No serious adverse events that could be attributed to the study drug were reported. The most common adverse events were headache and nausea/gastric-intestinal disturbance. One unrelated serious adverse event was reported (accident). One subject reported feeling faint, which was considered due to fasting. No clinical significant abnormalities in biochemistry and haematology profiles were reported. No antibodies to the medicinal products were found in any of the volunteers at the end of each study. In one of the studies, antibodies were not assessed (GF 8927).

#### *Clinical phase III fertility studies (GF 7648, GF 7927, GF 9073)*

No patient **died** in any of the Ovitrelle studies. Two serious adverse events in patients treated with 500 µg Ovitrelle, both consisting of OHSS, were reported that led to discontinuation of the study.

The most frequently reported treatment-associated AEs were injection site reactions (pain, bruising, injection site inflammation, injection site reaction), OHSS (3.6%), post-operative pain, abdominal pain, headache, and vomiting.

The applicant has performed an analysis of *adverse event dose-response* information. No dose-response related pattern of adverse events was noted in the phase I studies, that used doses ranging from 25 µg to 1,000 µg. In study GF 7927, both 250 µg and 500 µg Ovitrelle were administered as a single dose. Adverse events possibly or probably related to Ovitrelle were reported by 31/95 and 32/89 patients, respectively. Regarding most commonly reported adverse events, the percentage of patients reporting nausea, abdominal pain and cases of OHSS were higher in the 500 µg Ovitrelle group. Severe or life-threatening events were more common in the 500 µg group, mainly due to the higher number of OHSS cases.

#### **OHSS**

The main serious safety concern is the incidence of OHSS. Regarding the occurrence and severity of OHSS, no clear differences were noted between Ovitrelle 250 µg and Profasi 5,000 IU. In the one clinical phase III study (GF 7927) that compared Ovitrelle 250 µg with Ovitrelle 500 µg and Ovitrelle 500 µg with Profasi 10,000 IU, OHSS was recorded in 3 (3.2%) patients in the 250 µg r-hCG group, in 8 (9.0%) patients in the 500 µg which was judged as severe in two cases with discontinuation of treatment, and in 3 (3.1%) patients in the Profasi 10,000 IU group. These results indicate a dose-related increase in OHSS, which was not in the same range as noted in the Profasi 10,000 group. These results suggest a higher potency of r-hCG versus u-hCG. This suggestion might be supported by the statistically significant higher serum hCG levels observed under treatment with Ovitrelle in two of the three clinical phase III studies, although the values obtained differed between studies and the use of different entities (IU and µg) additionally made comparisons difficult.

#### ***Local tolerance***

Regarding local tolerance, specifically investigated in the one study that compared subcutaneous administration of Ovitrelle with subcutaneous administration of Profasi (GF 7648), significantly better tolerance of Ovitrelle was demonstrated, compared to the Profasi (u-hCG). These results can be explained to the higher purity of the recombinant protein in Ovitrelle.

#### ***Immunogenic reactions***

Regarding immunogenic reactions, all patients tested for anti-hCG antibodies after a single dose of Ovitrelle were negative. Therefore, it can be concluded that Ovitrelle is not immunogenic.

#### ***Laboratory findings***

No clinically significant changes from baseline in routine laboratory tests (haematology, clinical chemistry and urinalysis) were noted in the three fertility studies. However, in those women suffering from OHSS several laboratory abnormalities were recorded that were considered to be consistent with the presence of OHSS and therefore evaluated by the investigator as probably related to study drug.

### ***Drug-drug interactions***

Regarding drug-drug interactions, no evidence for a clinical significant drug interaction was found in any of the fertility studies. More than 90% of participants used concomitant medication in study GF 7927 and GF 7648, whereas in study GF 9073 concomitant medication was less than 16%. The most commonly used concomitant medication included antibiotics, analgesics/anaesthetics, and benzodiazepines.

## **5. Overall conclusions and benefit/risk assessment**

### ***Quality***

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Ovitrelle is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch to batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

### ***Preclinical pharmacology and toxicology***

Overall, pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of choriogonadotropin alfa to induce ovulation. Results from the toxicology programme did not raise particular concerns for the safe use of choriogonadotropin alfa.

### ***Clinical efficacy and safety***

The results from clinical studies support the use of choriogonadotropin alfa in the intended indications for which the dose recommendation is one vial of Ovitrelle 250 µg (equivalent to 6500 IU) to be administered 24 to 48 hours after optimal stimulation of follicular growth is achieved. The clinical data provided did not support a dose recommendation of 500 µg in these indications.

The safety data demonstrates that choriogonadotropin alfa is safe. The adverse events reported revealed no unexpected adverse events attributable to choriogonadotropin alfa.

The most common side effects are: application site disorders (local reaction/pain at injection site), general disorders (headache, tiredness), gastro-intestinal system disorders (vomiting/nausea, abdominal pain), and reproductive disorders (mild or moderate ovarian hyperstimulation syndrome). Uncommon side effects are: psychiatric disorders (depression, irritability, restlessness), gastro-intestinal system disorders (diarrhoea), and reproductive disorders (severe ovarian hyperstimulation syndrome, breast pain).

## **Benefit/risk assessment**

### ***Benefit***

Clinical studies have demonstrated the efficacy of choriogonadotropin alfa in the two proposed indications, i.e. treatment of women undergoing superovulation prior to assisted reproductive techniques such as *in vitro* fertilisation (IVF) and anovulatory or oligo-ovulatory women. Current treatment in these indications consists of urine derived human hCG.

For marketing authorisation of the r-hCG liquid formulation, the MAH submitted a new study on the local tolerability of this formulation in male New Zealand White rabbits. This study showed that local toxicity of the r-hCG liquid formulation and the r-hCG freeze-dried formulation was comparable, when injected by subcutaneous and intramuscular routes. A bioequivalence study was also submitted. In this study safety data were also gathered. Based on the pharmacokinetic variables of r-hCG it was shown that the calculated 90% confidence intervals were within the acceptance range for bioequivalence. The other pharmacokinetic variables were also comparable between the test product and the reference product.

**Risk**

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Ovitrelle is considered to be acceptable when used in accordance with the conditions defined in the SPC. Viral safety has been documented.

The safety data demonstrates that choriogonadotropin alfa is safe. The adverse events reported revealed no unexpected adverse events attributable to choriogonadotropin alfa.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Ovitrelle was favourable in the treatment of :

- *Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF):* Ovitrelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth.
- *Anovulatory or oligo-ovulatory women:* Ovitrelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory patients after stimulation of follicular growth.

The Committee for Proprietary Medicinal Products recommended the granting of a marketing authorisation for Ovitrelle, subject to the chemical, pharmaceutical and biological follow-up measures being undertaken by the MAH.