SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cetrotide. This scientific discussion has been updated until 1 March 2003. For information on changes after this date please refer to module 8B.

1. Introduction

For treatment of infertility in female patients with non-functional fallopian tubes, reconstructive surgery has been the only therapy for many years. Since new treatment possibilities have been developed over the past 20 years, including in vitro fertilisation and embryo transfer (IVF-ET) for infertility treatment in women with non-functional fallopian tubes, and intracytoplasmatic sperm injection (ICSI).

Pharmacological stimulation of follicular growth and ovulation induction are essential for production of high quality oocytes. Assisted reproduction techniques (ART) are used to help couples with fertility problems. The process is preceded by controlled ovarian stimulation (COS) with human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG). Human menopausal gonadotropin, containing FSH and LH, is used for stimulation of follicular growth, recombinant FSH (rec-FSH) has also been licensed for this indication. Human chorionic gonadotropin in doses of 5000 to 10000 IU is used to trigger ovulation in stimulated cycles. A premature LH surge and premature ovulation may lead to cancellation of the stimulated cycle. In order to avoid a premature LH surge, pituitary down regulation is employed in most centers.

The role of a hypothalamic peptide factor controlling the release of the gonadotropin luteinising hormone (LH) and follicle-stimulating hormone (FSH) was established in the early 1970's. Since then many analogues of gonadotropin releasing hormones (GnRH or LHRH) have been synthesised to enhance the stability and affinity of the natural peptide which has a very short half-life (3-6 minutes). For pituitary down regulation, chronic administration of these agonists results in a desensitisation (down regulation) of pituitary receptors and inhibition of gonadotropin and sex steroid secretion leading to a selective medical hypophysectomy and a so-called chemical castration. GnRH agonist treatment (often as a depot preparation) is started in the luteal phase of the cycle preceeding the treatment (stimulation) cycle. The routine use of GnRH agonists prior to in vitro fertilisation / embryo transfer and gamete intrafallopian transfer results in a lower cancellation rate of cycles suggesting an improved pregnancy rate.

LHRH-antagonists were also used instead of the agonists. They are devoid of the initial stimulation (flare up) and the treatment period can be shorter. A sufficient follicular stimulation may be achieved with lower doses of gonadotropins (hMG). However, many of the antagonists provoked histamine release, edema of the face and extremities, and anaphylactic reactions in rats and humans.

Cetrorelix, a decapeptide with a sequence derived from LHRH, is a LHRH-antagonist. It effectively inhibits the release of LH from the pituitary gland; sex hormone levels are suppressed to castration levels in men and women. Two different dosages have been investigated: multiple doses of 0.25 mg once daily and a single dose of 3 mg cetrorelix.

2. Chemical, pharmaceutical and biological aspects

Composition

Cetrotide is presented as lyophilised powder and solvent for solution for injection containing cetrorelix acetate equivalent respectively to 0.25 and 3.0 mg cetrorelix base. The main excipient consists of mannitol. Acetic acid and water for injection were used during the manufacturing process. Prior to subcutaneous injection, the powders are for reconstitution with 1 ml or 3 ml of water for injection, which are available in pre-filled syringes. All components with the exception of the active substance comply with relevant Ph.Eur. monographs. The composition of batches used in clinical trials is only different from the intended market formulation in the quantity of cetrorelix and mannitol. No overage of the active substance is introduced.

Container - The primary packaging material proposed for lyophilisated powders is Type I glass vials (2 ml or 4 ml) closed with a brombutyl rubber stopper and protected with an aluminium cap. The brombutyl rubber is stabilised against oxidation. The quality of vials and rubber stoppers meet with Ph.Eur. requirements, which has been confirmed by full specification with description of test methods used. The pre-filled syringes (Type I glass cartridge closed with rubber stoppers) used for water for injection has already been authorised in some Member States and are of acceptable quality. However, the shelf-life should be restricted to that agreed for the finished product.

Pharmaceutical development - Cetrorelix acetate is thermally labile and unstable in aqueous solution, therefore sterilisation by filtration and lyophilisation (freeze-drying) are considered to be justified. Cetrorelix in solution tends to aggregate and gel. Mannitol was chosen for building up an acceptable solid cake. In addition, it prevents sublimation during lyophilisation and guarantees an isotonic solution after reconstitution with water for injection. The mannitol concentration was fixed and optimised in the finished dosage form in order to obtain an isotonic solution after reconstitution for parenteral use.

Active substance

Cetrorelix acetate is a linear decapeptide with a molecular weight of 1431, which comprises five L-amino and five D-amino acids including 1-2 mol acetic acid par 1 mol peptide. It is a white amorphous powder and hygroscopic. Its solubility in water and in water/mannitol is approximately 8 mg/ml and 5 mg/ml, respectively.

Cetrorelix acetate presents no polymorphic forms. The evidence of its chemical structure has been adequately confirmed by the pathway of synthesis, by characterisation of the structure of the isolated key intermediates and of the active substance itself by elemental analysis, spectroscopic methods (ESI-MS, H^1NMR, C^{13}NMR, IR and UV), X-ray diffraction, optical rotation. Deduction of amino acid sequence and enantiomeric analysis were also performed to provide further supportive evidence of chemical structure.

Cetrorelix acetate is manufactured by approximately a 26-step synthesis with satisfactory in-process control of intermediates applied at key steps throughout. HPLC method was used for final purification.

Potential impurities have been considered, including a possible by-product of racemisation during synthesis, related substances, paladium and residual solvents. Specifications have been set for the synthesis starting materials and intermediates. They are in line with batch release data and batches used in preclinical and clinical studies. The sum of four stereoisomeric peptide impurities, which cannot be completely resolved altogether by HPLC, is specified as no more than 0.1%. Acceptable limits of 0.5% and 1.5%, respectively, were set for the sum of unknown impurities and the total sum of impurities. Residual solvents are also specified at a suitable level in agreement with CPMP/ICH guidance. Appropriate microbiological control is performed with a suitable limit for bioburden. All analytical methods for starting materials and intermediates have been adequately validated. Batch analysis data indicate suitable uniformity and batch-to-batch consistency.

The active substance in solid state was tested for up to 18 months under different temperatures and relative humidities. It was also stressed in solution, under the influence of pH, temperature and oxidative conditions. Increase of water can be observed, but chemical and microbiological stability was not affected. Photostability testing was adequately carried out. Potential degradation products remain within the proposed specifications. Overall, the data support the re-test period of 18 months under the proposed storage conditions.

Other ingredients

The manufacture of water for injection was carried-out in a 6-step distillation process. Satisfactory information has been provided on the excipients which are all of Ph.Eur. quality.

Product development and finished product

Manufacture, *control and validation* - Bulk solution is filtered and pre-sterilisation is applied. Aseptic filling into sterile and depyrogenised vials is performed with a second sterile filtration before filling, then lyophilisation of the solution under aseptic conditions is carried-out. The vials are fitted with sterile stoppers and caps. Visual control of all vials is performed.

In-process controls are set up and their parameters are specified. Aseptic filling process and routine environmental controls are also performed and validated. Relevant microbiological control includes bioburden of the solution prior to filtration. Maximum holding times are validated.

The critical stages in the manufacturing process have been validated. Results from production scale batch analyses showed that all batches complied with specifications and demonstrated acceptable batch to batch consistency.

Product specification - The specification for content of active substance at release is 95 – 105% of the nomination value, and at least 90% at the end of shelf-life. Content uniformity is in accordance with the Ph.Eur. requirement. Related impurities are controlled at release and end of shelf-life based on batch analytical results and stability results, and validated with reference to preclinical studies.

Other tests include pH, colour, average filling, turbidity of reconstituted solution, water and acetate content, bacterial endotoxin and sterility. In addition, injectable amount with regard to withdrawal volume has been investigated and mentioned in the SPC. All control methods have been validated in a satisfactory way.

Stability of the product

Stability data up to 24 months are available for 3 batches of each strength. Different storage conditions have been studied: -10ºC, 8ºC, 25ºC/60%RH and 30ºC/70%RH (for up to 24 months), 40ºC/75%RH (6 months) and light cabinet (3 months). Results have been generated by validated methods and support the (un-opened) shelf-life stated in the SPC, i.e. 2 years when stored at temperatures below to 25°C in the outer carton. In addition, after reconstitution stability tests were conducted, which indicate that both formulations, as mentioned in the SPC, should be used immediately.

In summary, Cetrotide 0.25 mg and 3 mg powder and solvent for solution for injection are conventionally formulated and manufactured using standard pharmaceutical technology. The chemical-pharmaceutical dossier is adequately documented and generally acceptable. The company was however requested to provide, within the agreed timeframe, additional information/data which have not been satisfactorily resolved; these are defined in the follow-up measures as listed in the company's undertaking letter (see section II.3 of this report).

3. Toxico-pharmacological aspects

Pharmacodynamics

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist, which competes reversibly with the hormone in binding to the membrane receptors on pituitary cells. Due to this mode of action, cetrorelix dose-dependently inhibits the secretion of two gonadotropins luteinising hormone (LH) and to a lesser degree, follicle stimulating hormone (FSH) from the pituitary gland in mice, rats and cynomolgus monkeys. The onset of suppression is almost immediate and there is no apparent initial stimulatory effect, i.e. no “flare-up”. The suppression is maintained by continuous treatment and has been shown to be reversible after discontinuation of the treatment. Given in sufficiently high doses, a reversible cessation of reproductive function is observed in both female and male animals.

Cetrorelix binds with high affinity to LHRH receptors, and labelled LHRH was shown to be displaced from the two classes of LHRH receptors by the compound. *In vitro*, cetrorelix dose-dependently inhibited the LHRH-mediated LH release in perfused rat pituitary cell systems. Further, in a recently established *in vitro* assay, cetrorelix proved to be a high affinity antagonist at the LHRH-receptor and dose-dependently blocked the signal transduction induced by LHRH.

In vivo, cetrorelix effectively blocked ovulation in female rats. It suppressed the preovulatory LH-peak as well as the FSH-peaks. Cetrorelix markedly decreased plasma LH concentrations and to a lesser

degree FSH concentrations in ovariectomized female rats. All effects were reversible. In castrated male rats, cetrorelix induced a dose dependent suppression of the secretion of LH. High doses resulted in a dramatic fall of serum testosterone to castration levels at 6 hours after injection in intact males. Thereafter, testosterone levels only slowly recovered. Even though the initial fall of plasma testosterone requires rather high doses of cetrorelix, complete and continuous suppression can be maintained by remarkably lower maintenance doses. Cetrorelix was also able to block LHRH-agonist induced LH response in male rats. The LHRH-antagonistic effects of cetrorelix were confirmed in the primate *Macaca fascicularis*.

The main metabolite of cetrorelix in the rat bile was identified as being the heptapeptide(1-7). This metabolite was pharmacologically inactive in rats, in terms of testosterone suppression.

Cetrorelix produced growth inhibition in both the rat DMBA breast cancer model and mouse MXT mammary adenocarcinoma model. In addition, the efficacy of cetrorelix was confirmed in *other in vitro* and *in vivo* tumor models, e.g. chemically-induced pancreatic cancer, hormone-independent prostatic cancer, human ovarian- and endometrial cancer models.

The histamine releasing potential of cetrorelix is very low. Cetrorelix caused histamine release from isolated rat mast cells only after concentrations of >0.9 µg/ml. In clinical situations, single s.c. doses of 3 mg of cetrorelix produce plasma levels of about 30 ng/ml. No limiting anaphylactoid reactions were observed within preclinical testing.

Cetrorelix shows a favourable safety-profile. It had no effects on the cardio-vascular parameters of pigs. Similarly, no effects on the respiratory function of anaesthetised guinea pigs or rats were observed. Furthermore, cetrorelix induced no gastric erosions in rats and was devoid of effects on the gastro-intestinal transit, spontaneous motor activity and motor co-ordination in mice.

Cetrorelix had no effect on the hexobarbital-induced or ethanol-induced loss of righting reflex in male mice. No other preclinical drug interaction studies have been performed.

Pharmacokinetics

Pharmacokinetic studies were performed predominantly in rats and dogs. Absorption from the s.c. injection site was rapid and complete and there were no differences in absorption with regard to sex or species. A linear relationship between dose and plasma AUC was evident. Distribution of cetrorelix was rapid. Main target organs were the kidney, liver, small intestine and organs containing the LHRH receptor (pituitary gland, ovaries). Plasma protein binding amounted to 86%. Elimination from most tissues was rapid and occurred predominantly within 48h. Half-lives of ≥100 h were observed mainly in organs of elimination (liver, kidney), spleen and in the organs containing LHRH binding sites. Cetrorelix crosses the placenta only to a low extent. The distribution of cetrorelix or its metabolites into milk was not investigated. Cetrorelix is excreted unchanged into urine and after metabolism by peptidases into bile. The terminal half-lives in rats after i.v. and s.c. administration were 1-2 h and 7-14 h, respectively, indicating that absorption is the rate limiting step for elimination. In humans, the terminal half-life values after i.v. and s.c. administration were 8-9 h and 24-40 h, respectively. Studies in healthy volunteers indicate that cetrorelix is excreted in a similar manner in humans, rats and dogs.

No significant differences in the pharmacokinetic parameters between the repeated-dose study and the single-dose data were found. Furthermore, no accumulation of cetrorelix occurred following repeated s.c. administration.

Toxicology

Single dose toxicity of cetrorelix after oral and i.p. administration was studied in rats and mice. The acute oral toxicity was low. After i.p. injection, doses ≥21.5 mg/kg caused reduced or slow movement, sunken sides, cyanosis of the skin and co-ordination disturbances. 68.1 mg/kg was determined as the minimal lethal dose.

Repeated-dose toxicity In the five repeated-dose toxicity studies of up to 26 weeks, performed on rats and dogs, daily s.c. injections of up to 0.5 mg/kg of cetrorelix were well tolerated. No particular organ toxicity was determined. All observed changes appeared to be related to the pharmacological action of cetrorelix and, thus are secondary to suppression of hormone levels. Minimal local irritant effects at the injection sites are partially related to a deposition and an accumulation of the drug in macrophages. All the findings were reversible or tended to be reversed during off-dose.

Genotoxicity Standard battery of *in vitro* and *in vivo* genotoxicity tests was carried out. No evidence of mutagenic or clastogenic potential was found and it can be concluded that cetrorelix will not exert genotoxic activities under therapeutic conditions.

Carcinogenicity No carcinogenicity studies have been performed.

Reproductive and development toxicity studies Cetrorelix expectedly induced a dose-related suppression of fertility, reproductive performance and pregnancy in female rats and a dose-related suppression of fertility in male rats. The effects were reversible after cessation of treatment. No treatment-related foetal abnormalities were detected in rats or in rabbits when the drug was administered during the relative sensitive phase of organogenesis.

Local tolerance i.v., s.c. and intramuscular injections to beagle dogs were generally well tolerated with no clinically relevant signs of local irritation.

Special toxicity studies Cetrorelix did not induce sensitisation in the guinea pig Maximization test.

Summary and conclusion on preclinical pharmacology and toxicology:

Cetrorelix is a potent antagonist of LHRH in various *in vitro* and animal models and binds competitively and with high affinity to pituitary LHRH-receptors. The subsequent LH-suppression is induced within a few hours after the start of treatment and thus avoids the flare-up effect. A dose-dependent and reversible suppression of the secretion of gonadotropins, especially LH, from the pituitary gland ensues resulting in a cessation of reproductive function both in female and male animals.

Cetrorelix shows a favourable safety-profile and no limiting anaphylactoid reactions were observed during preclinical testing. The pharmacokinetics of cetrorelix have been well characterised in rats and dogs. Findings in toxicity studies appear to be related to the pharmacological actions of cetrorelix and are thus secondary to suppression of hormone levels. No teratogenicity was detected and mutagenicity tests were also negative. No carcinogenicity studies have been performed and none are necessary given the short duration of intended use. The doses used in repeated-dose and reproductive toxicity studies provide an acceptable safety margin, in terms of C_{max} and AUC, for the proposed dose regimen. Overall, the risk-benefit ratio is considered positive and the preclinical data revealed no special risk for human.

4. Clinical aspects

The core clinical programme, consisting of 9 Phase II/III clinical studies where a total of 878 patients were given cetrorelix acetate (CET), was aimed at evaluating the efficacy and safety of CET for the prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by assisted reproductive techniques (COS/ART). There were four exploratory studies (0008, 0009b, 0012 and IC93005), two dose finding studies (2986 and 2997) and three therapeutic confirmatory studies (3010, 3020 and 3030). In addition, a total of 14 Phase I clinical pharmacology studies were submitted, where 137 healthy males and 71 healthy females were enrolled. Studies were performed in accordance with GCP standards.

Due to the nature of the treatments and the manner of use of this medicinal product, most studies were open label. Both single and multiple dose regimens were investigated.

(1) **Human pharmacology**

(2) **Pharmacodynamics** - Cetrotide (CET) is a LHRH antagonist which competes with endogenous LHRH for receptors on pituitary cells. The evidence for receptor binding was derived from animal studies. The effect of cetrorelix in healthy male or female volunteers was investigated in 8 pharmacodynamic studies.

In female volunteers (at doses of cetrorelix 0.25 and 0.5 mg) a rapid dose dependent suppression of LH, FSH and estradiol (E_2) were observed, the duration of the effect (suppression of LH) was up to 12 hours and increased with increasing dosages. Single dose administration (3.0 or 5.0 mg) during the early follicular phase (estradiol exceeded 150 pg/ml) delayed the spontaneous LH surge by at least 3 days. Repeated administration (0.5 or 1.0 mg cetrorelix) resulted in constant suppression of LH, FSH

and an estradiol nadir of 12 pg/ml, whereas during repeated administration of 0.25 mg cetrorelix, LH and estradiol were suppressed initially and then tended to increase.

In male volunteers the suppressive effect of cetrorelix on LH, FSH and testosterone was observed, both with single doses (0.25 and up to 5.0 mg) and multiple doses (up to 10.0 mg). These effects were dose-related. At the higher dose of 10 mg, the testosterone suppression reached castration level (<2 mmol/l). After 3 mg cetrorelix, the resulting suppression of LH was more than 50 % decrease from baseline and the testosterone suppression lasted 30 hours. The duration of suppression was dose dependent.

GnRH stimulation was not totally suppressed by cetrorelix, but GnRH stimulation of FSH was less pronounced following treatment with cetrorelix. The higher doses of 15 and 20 mg did not enhance the suppressive effect. The most common adverse events observed in phase I studies were local injection site reactions. There was also some suggestion of decrease in systolic as well as diastolic blood pressure and an increase in heart rate in the phase I studies.

(3) **Pharmacokinetics** - Cetrorelix in human plasma was measured by radioimmunoassay, and HPLC was employed for measurement in urine. These methods were adequately validated.

Following subcutaneous injection, the absolute bioavailability of cetrorelix was approximately 85% in both males and females. The apparent volume of distribution was 1.16 ± 0.29 l/kg in females and 1.02 ± 0.33 l/kg in males. The terminal half-life ($t_{1/2}$) was about 10 hours after i.v. and 30 hours after subcutaneous injection with a trend towards lower values in female. Protein binding in human plasma was around 85%. Linear pharmacokinetics were observed following both single (0.25, 0.5 and 1.00 mg) and multiple dose administration (0.25 to 1.00 mg). The pharmacokinetics were linear up to a 3 mg dose.

Cetrorelix is metabolised by peptidases. Small amounts of metabolites (1-9 nonapeptide, 1-7 heptapeptide, 1-6 heptapeptide and 1-4 tetrapeptide) were detected in animal urine (rat, dog) in addition to unchanged CET, whereas only unchanged CET has been detected in human urine. Following subcutaneous injection, 3.5-4.0% of the administered dose appeared unchanged in urine, no potential metabolite (1-7 heptapeptide) was detected. No indication of accumulation has been reported.

Pharmacokinetic studies in special populations (i.e. elderly, children, subject with moderate to severe renal or hepatic impairment) have not been performed. Use in elderly and subjects with moderate to severe renal and hepatic impairment are contraindicated in the SPC. Due to the nature of its indication, Cetrotide is unlikely to be used in children.

There were no data on drug interactions. Interactions with hMG and hCG have not been observed, plasma levels of cetrorelix during follicular stimulation did not differ from plasma levels in healthy individuals. *In vitro* investigations indicated no evidence of cetrorelix metabolism by cytochrome P450 enzymes, glucuronyltransferases or other conjugating enzymes.

Efficacy

In all phase II/III studies, the therapeutic procedure for controlled ovarian stimulation (COS) was nearly identical. In the phase III studies treatment with hMG started on day 2 of the menstrual cycle with daily doses of 150 IU hMG (2 ampoules, each containing 75 IU FSH and 75 IU LH) given i.m. From day 6 of hMG treatment, the dose of hMG was adjusted according to follicular maturation criteria. On the same day the first dose of cetrorelix was given s.c. into the lower abdominal wall around the umbilicus. In case of daily cetrorelix administration the last dose was given on the day of hCG. As soon as at least one follicle with a diameter of 20 mm was observed or E_2 exceeded 1200 pg/ml, treatment with hMG was stopped and hCG 10000 IU were administered i.m. Oocyte retrieval took place 30-36 hours later

Patient population – Healthy female partners of infertile couples aged between 18 and 39 years (suffering from sterility due to tubal dysfunction) were included. Further inclusion criteria were a normal menstrual cycle (24-35 days), normal uterus and at least one functioning ovary, patients with elevated FSH levels at screening were excluded. The usual exclusion criteria for ART were applied.

Efficacy parameters – The primary endpoint in most studies was prevention of premature LH surge (defined in terms of LH $\geq$ 10 IU/l and PROG $\geq$ 1ng/ml) but the definition of LH surge varied between different study protocols.

In therapeutic confirmatory studies (i.e. 3010 and 3020), the primary objective was the prevention of premature LH surges defined in terms of LH and progesterone (PROG) levels. The statistical section of the protocol indicated that a patient will be considered as a responder "if hCG day is reached" (meaning administration of hCG) and it will be the primary variable.

Secondary variables comprised endocrine profiles of LH, FSH, E_2 and PROG during the procedure, number and size of follicles, number and quality of oocytes and embryos, duration of stimulation and dose of hMG, outcome of the procedure in terms of pregnancy and birth rate, ovarian cyst formation before stimulation period and luteal phase support.

Pregnancy and delivery data after COS/ART employing the LHRH-antagonist cetrorelix were also analysed in 6 dose-finding phase II (with a total of 229 patients receiving cetrorelix) and 3 phase III studies (649 patients receiving cetrorelix).

Exploratory studies - Four exploratory studies (0008, 0009b, 0012 and IC93005) were conducted using different dosage regimens of CET: single dose (3 mg or 5 mg) and multiple doses (0.5 mg or 1 mg/day; twice 3 or 5 mg; 1 and 3 mg/day followed by 5 mg or 1 mg/day). No LH surge was reported in either dose group. There was no effect of CET on FSH, PROG or E_2.

Dose finding **-** Two dose finding studies (2986, 2997) were conducted to evaluate the minimal effective single dose and the efficacy of multiple doses of cetrorelix to prevent premature ovulation in patients undergoing COS/ART.

A total of 65 patients were recruited (study 2986) to receive a single dose of either 2 or 3 mg CET. While 3 mg dose was constantly effective in preventing LH surge after 4 days, the 2 mg dose effect was not sustained showing a tendency of LH increase after 3 days.

In the multiple dose study (2997), ninety patients were included, who either received a starting dose of 0.5 mg/day (with eventually a down-titration to lower dose), 0.25 mg or 0.1 mg/day. None of the patients in CET dose groups of 0.25 mg or 0.5 mg experienced LH surges while one patient in 0.1 mg dose group showed an LH surge. Hormonal levels of FSH, E_2 and PROG were not affected by cetrorelix. The minimal dose of 0.1 mg cetrorelix proved to be not sufficiently effective, and therefore was no longer administered.

Consequently, 0.25 mg cetrorelix was shown to be the minimum effective dose. Two dosage regimens were proposed for Phase III studies: (1) daily dose of 0.25 mg starting on day 5 or 6 of hMG; (2) a single dose of 3 mg on day 7 of hMG, eventually followed by once daily 0.25 mg after 4 days. Both regimens are administered until ovulation induction.

Therapeutic confirmatory - Three multicentre prospective studies were conducted to support the claimed indication, one uncontrolled and two comparing cetrorelix (CET) and LHRH-agonists (buserelin and triptorelin). Numbers of patients were based on estimating the response rate on cetrorelix, based on a target response rate of 95%, with a slightly larger 5% possible error. Efficacy evaluation based on the intention to treat (ITT) population was given. The most frequent posology was 0.25 mg cetrorelix starting on day 6 of hMG (study 3020) (n=346) or on day 5-6 (study 3010) (n=188) of hMG-stimulation. The single dose of 3 mg started on day 7 of hMG (study 3030) (n=115) or earlier, when the E_2-levels exceeded 400 pg/ml. The reference treatments were buserelin (BUS) 0.15 mg intra-nasal administration four times daily (starting on day 18-22 of the preceding cycle) and triptorelin (TRI) 3.75 mg depot single intramuscular administrations.

<u>*Study 3010*</u> was a randomised, parallel group, controlled trial, which compared daily doses of cetrorelix with buserelin in the prevention of premature LH surges in patients undergoing COS/ART. A total of 293 patients were randomised and 273 patients were evaluable for efficacy on ITT basis (188 received cetrorelix and 85 buserelin).

The mean duration of cetrorelix treatment was 5.7 days. Success rate, defined as absence of LH surge, was 95.2% for CET group and 98% of patients on buserelin. On an ITT basis and in terms of reaching the day of hCG, the success rate was 96.3% in CET group and 90.6% in the buserelin group. Increases of LH above 10 IU/l without increase of progesterone occurred in 10.1% (19) of patients in the CET group versus 4.7% (3) in the buserelin group. However, some of these LH increases did not lead to failure to administer hCG or to complete fertilisation procedures, and hence they may not have clinical significance. There was no effect of either treatment on FSH. In buserelin group, levels of LH and E_2

were lower on hMG day 1 as well as day 6, but E_2 levels were higher on the day of hCG which may be caused by a higher number of small follicles in this group.

Study 3020 was an uncontrolled trial aimed at investigating the efficacy and safety of daily doses of cetrorelix in prevention of premature LH surges during controlled ovarian stimulation. The multiple dosing schedule used was similar to the study 3010.

The primary efficacy variable was defined as reaching the day of hCG but the rate of premature LH surges was also analysed. Overall, 352 patients were screened and 346 patients were evaluable as the intention to treat population.

The mean duration of cetrorelix treatment was 5.7 days, with an average of 1 to 1.5 mg cetrorelix administered. The duration of follicular stimulation was 10.4 (6-19) days. Surges of LH were observed in 12 patients of the ITT population, in eight of which fertilisation and embryo transfer were possible and one woman became pregnant. Increase of LH (= 10 UI/l) without concomitant progesterone increase was also observed in 27 patients. The success rate for absence of LH surge was 96.5% and for reaching hCG day was 96.2% of ITT analysis (with a lower bound for the 95% confidence limit of 94.1%, which is slightly below the targeted 95%)**.**

A continuous and homogenous follicle development was observed between day 6 of hMG and the day of hCG. The number and quality of obtained embryos is in accordance with the results of controlled studies.

Study 3030 was a parallel group study comparing a single dose of cetrorelix and a triptorelin depot. A total of 169 patients was randomised. There were 151 patients (115 cetrorelix and 36 triptorelin) in the ITT analysis. A single dose of each treatment was given at different times in an open fashion. The primary endpoint was planned to be the occurrence of premature LH surges defined in terms of LH and progesterone levels and occurring after day 5 of hMG.

Only 11 patients (9.6%) received one or two additional doses of cetrorelix 0.25 mg. The mean duration of follicular stimulation was 9.4 days for the cetrorelix group and 10.7 days for the triptorelin group, 24.3 vs. 35.6 ampoules (mean) of hMG were administered.

Levels of LH above 10 IU/l occurred in 18 patients in the CET group and in one patient in the TRI group. These LH increases in CET group were however observed before the administration of the study medication but not after the administration of cetrorelix. Taking the LH surge in terms of luteinising hormone levels alone led to a response rate of 84.3% for cetrorelix. The ITT incidence of the responders was 97.4% in CET group and 97.2% in TRI group.

On the day of hCG, the number of medium sized follicles (15-17 mm) was slightly higher in the triptorelin group. No differences were observed between the groups concerning FSH, LH and PROG, but E_2 levels on hCG day were higher in TRI group which may be attributed to higher number of follicles in TRI group.

Luteal support - In COS/ART programmes using LHRH-agonists for down-regulation of endogenous gonadotrophin production, luteal phase support is generally recommended as it is believed that the treatment may result in luteal phase defects. Controlled ovarian stimulation (hMG and hCG) results in a decrease of LH levels to the detection limit on the day of embryo transfer (ET), this has been shown in patients treated with cetrorelix, buserelin or triptorelin. No final conclusions are possible, whether the suppression depends on the LHRH-analogues or on long-term effect of hCG. In all clinical studies, luteal phase support was given according to the rules of the centre, in most cases progesterone, few centres administered hCG or a combination of progesterone and hCG. A recommendation concerning luteal support according to the reproductive medical centre's practice is mentioned in the SPC**.**

Evaluation of pregnancies and deliveries - Different ART procedures were used in the studies. IVF/ET and ICSI are highly sophisticated procedures, which differ more or less from centre to centre; IVF and ICSI resulted in a similar pregnancy rate which was between 20 and 27% in cetrorelix patients. The following table gives an overview on patients reaching the day of hCG, on patients with ovum pick-up (OPU), patients with ET, pregnancies and deliveries:

Study no	Treatm	N (ITT)	day of hCG (%)	OPU (%)	ET (%)	preg. (%)	Deliv (%)/life birth (%)*
Total Phase II	Cet	229	225 (98)	222 (96)	210 (91)	72 (31)	51 (22) / 62 (27)
Study 3010	Cet	188	181 (96)	178 (95)	157 (84)	45 (24)	32 (17) / 39(20)
	Bus	85	77 (91)	77 (91)	67 (79)	25 (29)	19 (22) / 22 (26)
Study 3020	Cet	346	333 (96)	324 (94)	297 (86)	72 (21)	50 (14) / 68 (20)
Study 3030	Cet	115	113 (98)	113 (98)	99 (86)	30 (26)	25 (22) / 32 (28)
	Trip	36	36 (100)	36 (100)	33 (92)	14 (39)	9 (25) / 13 (36)
Total phase III	Cet	649	627 (97)	615 (95)	553 (85)	147 (23)	107 (16) / 139 (21)
	Control	121	113 (93)	113 (93)	100 (83)	39 (32)	28 (23) / 35 (29)

** including data until July 1998*

Few of the cycles were replacement cycles in which no cetrorelix treatment was given; in these cases a frozen embryo originating from a cycle during which stimulation with hMG and treatment with cetrorelix or comparator drug took place, was transferred.

No firm conclusion can be drawn concerning the effectiveness of the cryopreservation programme. However, the limited data on frozen-thawed cycles did not show a detrimental effect.

In phase II studies, 59 pregnancies (25%) occurred after the first embryo transfer and additional 13 pregnancies were achieved after the first or second replacement of frozen and thawed embryos, showing an overall pregnancy success rate of 31%. A total of 62 children were born.

In phase III, the results of comparative studies in terms of pregnancies and deliveries suggest a higher pregnancy (9% difference) and birth rate under treatment with LHRH-agonists. There is no statistical interpretation for the different pregnancy rates.

Miscarriages occurred in approximately 16% of the pregnancies in the phase II and III studies; pregnancies achieved in replacement cycles had a higher abortion rate of more than 23%. Four abortions in the phase II studies (three of them in replacement cycles) were performed due to anatomical defects or chromosomal abnormalities. One anatomical defect and no chromosomal abnormality were reported for cetrorelix in phase III studies. Ectopic pregnancies occurred in eight cases of 219 pregnancies.

The comparison of the pregnancy rates in cetrorelix and buserelin/triptorelin treated patients with the published data shows an exceptionally high pregnancy rate in triptorelin treated patients and rates for cetrorelix, which are comparable with published literature. A benefit comparable to established treatments can be assumed for cetrorelix.

Summary on efficacy:

Two dosage regimens have been confirmed. CET 0.25 mg as multiple dose and CET 3 mg as single dose are effective in preventing LH surges. Treatment with daily doses of 0.25 mg starting (studies 3010 and 3020) on day 5-6 of follicle stimulation or with a single dose of 3 mg (study 3030) on day 7 of follicle stimulation (in some cases followed by daily injection of 0.25 mg after 4 days) until ovulation induction is recommended to prevent an LH surge. On either efficacy criteria, absence of LH surge or day of hCG, CET was successful in the majority of patients.

In clinical trials, cetrorelix was used with human menopausal gonadotropin (hMG), however limited experience with recombinant FSH (61 patients undergoing COS/ART in whom ovarian stimulation with rec-FSH took place, 50% of whom received cetrorelix 3 mg single dose and another 50% of whom cetrorelix multiple doses of 0.25 mg) suggested similar efficacy. This was addressed in the SPC.

There is limited experience up to now with the administration of cetrorelix 3 mg during a repeated ovarian stimulation procedure. Therefore cetrorelix 3 mg should be used in repeated cycles only after careful risk/benefit evaluation.

Safety

The assessment of the safety of cetrorelix is based on the integrated summary including database from 878 female (during 881 stimulated cycles) and 196 male subjects exposed to cetrorelix, 125 females exposed to reference treatments and 39 males exposed to placebo.

Discontinuation - Two patients discontinued treatment due to adverse events, one patient on CET had injection site reaction, and another on placebo had urticaria.

Adverse events - The most common adverse events were injection site reactions (with an incidence of 9.4% following multiple injections of 0.25 mg cetrorelix), e.g. erythema, inflammatory reactions, bruising, red plaque, itching, swelling and induration. The incidence of these events was higher in females in phase I studies and in single dose studies. Among female subjects, other common adverse events observed in phase I studies were hot flushes, menstrual disorder, inter-menstrual bleeding and pruritus; in addition to injection site reaction, those reported in COS/ART (phase II /III) studies were nausea, headache, hot flushes, menstrual and ovarian disorder. In male subjects with benign prostatic hyperplasia (C2980) treated with cetrorelix, hot flushes and impotence were frequently reported; a dose-related effect was noted. Decreased libido was also reported by both male and female subjects.

The events reported as likely causally related were injection site reaction, nausea, pruritus and headache. They are mentioned in the SPC.

Serious adverse events - Eight serious adverse events were reported, 5 of them were ovarian hyperstimulation syndromes (OHSS). The 3 other cases included one patient with urinary infection, one patient with diarrhoea, nausea and abdominal pain, and one patient with a probable abdominal infection and distension by gas.

In men with benign prostatic hyperplasia, the serious events observed were cardiac distress (in subject with a history of coronary artery disease), chest pain (assessed as non related), myocardial infarction (in patient with a history of myocardial infarction 3 and half months after study drug medication) and elective coronary revascularisation. The assessment of causal relationship revealed in all cases of serious adverse events that a causal relationship was unlikely.

Laboratory parameters - In phase I studies, urea increased by 12.7%, triglycerides by 42.8%, HDL by 14.4% and platelets by 9%. In COS/ART studies in females, no significant differences were noted between CET group and reference therapy – LHRH agonist.

In other studies and in males, CET group showed significant increase in SGOT (14.5%), SGPT (31.9%), BUN (11%), HDL-cholesterol (9.4%) and cholesterol (5.7%).

Limited data provided on BUN showed no trend of rising BUN following cetrorelix treatment. Although there was no serious safety concerns regarding liver function tests, a clear trend was noted for late increase in liver enzymes and alkaline phoshatase. Their association with cetrorelix cannot entirely be ruled out.

Repeated administration - There was limited data available on repeated administration, it is unknown whether the efficacy remains unchanged or whether sensitisation has been observed. An appropriate statement is included in the SPC.

The safety data of cetrorelix 3 mg dose did not show a higher number of adverse events or more serious adverse events except for injection site reactions, which were not considered as serious.

Post-marketing experience - The evaluation of 3rd Periodic Safety Update Report signals a higher risk of hypersensitivity reactions at the time of first injection of Cetrotide, which in some cases reached the severity of an anaphylactic reaction. At present, occurrence of this kind of reaction cannot be excluded

for subsequent injections. There is a relationship between previous allergic predisposition and hypersensitivity to Cetrotide (all reported cases had a history of allergic predisposition). Appropriate information have been included in the SPC and PL.

Overall risk/benefit analysis

In therapeutic confirmatory studies, there was no group-comparative analysis planned initially for the target parameter to show non-inferiority of cetrorelix by the means of significance tests and confidence intervals (95%) for the appropriate parameters of all studies. Subsequently, confidence intervals for the demonstration of non-inferiority of cetrorelix in comparison to controls with a posteriori fixed margin of 10% were used. However, ITT analysis of the results of these studies in terms of their cetrorelix arms, response rates of above 95% were achieved for the prevention of premature LH surges and for reaching the hCG day. The response rates were confirmed by the uncontrolled study of multiple dosing schedule. This may be regarded as evidence of efficacy.

In two studies with a sample size of 303 cetrorelix patients, a parallel comparison of cetrorelix vs buserelin and vs triptorelin depot has been carried out, the results show a very similar effective prevention of LH-surges for both treatments. In these comparative studies, the results in terms of pregnancies and deliveries are lower for cetrorelix. With respect to some secondary efficacy endpoints, the results show partly a tendency towards disfavouring CET in comparison to BUS and TRI. In phase III studies, centre effects were observed. Furthermore, differences in prognostic factors at baseline (history of pregnancies, male factors) to achieve pregnancy could also account for the inferior rate following treatment with cetrorelix.

The comparison with published data, in terms of pregnancy rates, of cetrorelix and buserelin/triptorelin treated patients shows an exceptionally high pregnancy rate in triptorelin treated patients, and the COS/ART procedure with cetrorelix results in pregnancy rates similar to those reported in literature for ART employing long protocols with LHRH-agonists.

Injection site reaction and ovarian hyperstimulation syndromes were identified as main adverse events. The injection site reaction would not alter the risk:benefit ratio of the product and OHSS is not an unexpected consequence of COS. Headache and nausea were not considered serious in nature. Amongst laboratory abnormalities, increased levels of HDL-cholesterol, triglyceride, cholesterol, BUN, and abnormal liver function test were notable. Patients with moderate to severe renal and hepatic impairment are contraindicated in the SPC. The number of investigated women (over 800 treated with cetrorelix) is considered sufficient to detect an adverse reaction, which occur at a frequency of 0.5%.

Overall, a benefit comparable to established treatments can be assumed for cetrorelix. A LH-surge can be avoided by a daily dose of 0.25 mg starting from day 5-6 of hMG stimulation or a single dose of 3 mg given on the 7th day of follicular stimulation. If an LH surge has to be prevented for more than 4 days, additional injections of 0.25 mg daily are recommended starting 96 hours after 3 mg injection until the day of ovulation induction.

5. Conclusion

The quality of Cetrotide 0.25 mg and 3 mg powder and solvent for solution for injection, as demonstrated in the chemical, pharmaceutical documentation, is generally acceptable. Additional data was requested as defined in list of follow-up measures to be provided within an agreed timeframe.

The preclinical pharmacodynamic studies have adequately demonstrated that cetrorelix is a potent antagonist of LHRH in various in vitro and animal models and binds competitively and with high affinity to pituitary LHRH-receptors. Findings in toxicity studies appear to be related to the pharmacological actions of cetrorelix and thus secondary to suppression of hormone levels. Overall, the preclinical data do not raise special concerns for human safety.

The clinical efficacy confirmed that LHRH-antagonist, cetrorelix, effectively inhibits the release of LH from the pituitary gland. It has not been investigated prospectively nor in a confirmative approach whether the efficacy of cetrorelix is equivalent to the efficacy of LHRH-analogues. However, the efficacy of cetrorelix is comparable with published literature for LHRH-analogues in terms of achieved pregnancies. In a direct comparison of cetrorelix versus buserelin and versus triptorelin depot, its

efficacy was very similar regarding prevention of LH surges, however, it was inferior in terms of pregnancy and delivery rates.

The majority of the reported adverse events were injection site reactions, e.g. reddening, itching, swelling, induration. Systemic adverse events were rare, e.g. nausea, pruritus and headache. The administration of cetrorelix outside COS (i.e. in healthy women) results in symptoms of estrogen deficiency, withdrawal bleeding and hot flushes, whereas these symptoms are not expected in COS patients. Laboratory parameters did not change in a relevant manner. There were no serious safety concerns with regards to liver function tests, although a clear trend was noted for late increase in liver enzymes and alkaline phosphatase. The SPC includes appropriate contraindications regarding moderate to severe renal and hepatic impairments.

Taking into consideration the data provided, the overall safety issues and the benefit/risk ratio, cetrorelix is considered to be a safe and effective alternative for the prevention of premature ovulation in patients undergoing a controlled ovarian stimulation. The CPMP considered the benefit to risk assessment positive and recommended the granting of a Marketing Authorisation for all strengths and presentations of this medicinal product. The product is authorised for the indication 'Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

Abbreviations:

COS/ART: Controlled ovarian stimulation/Assisted reproduction technique

LH: Luteinising hormone

LHRH: Luteinising hormone releasing hormone

FSH: Follicle stimulating hormone

GnRH: Gonadotropin releasing hormone

HCG: Human chorionic gonadotropin

HMG: Human menopausal gonadotropin

PROG: Progesterone

E_2: Estradiol

OPU: Ovum pick-up

OHSS: Ovarian hyperstimulation syndromes

ET: Embryo transfer