SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 January 2003. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Puregon contains the active substance, follitropin beta (INN), a recombinant human Follicle Stimulating Hormone (r-hFSH).

This medicinal product is referred to List A in the Annex of the Council Regulation (EEC) 2309/93 as it is developed via recombinant DNA technology.

FSH is a gonadotropic hormone produced by the anterior lobe of the mammalian pituitary gland. It is a heterodimeric glycoprotein consisting of two subunits, a 92-amino acid α-chain (common to other glycoprotein hormones) and a specific 111-amino acid β-chain. The hormone can exist in a variety of isoforms and its activity varies according to the degree of glycosylation. FSH is indispensable for normal female and male gamete growth and maturation, and normal gonadal steroid production. Deficient endogenous production of FSH is a known cause of infertility. Administration of exogenous gonadotropins is used to treat infertility, and gonadotropins extracted from the urine of postmenopausal women have been on the market for over 30 years.

The manufacture of gonadotropins via recombinant DNA technology is independent of the collection of large volumes of urine and results in a highly pure product. It is devoid of infectious or pharmacological contaminants such as LH, proteinacious or potentially allergenic materials.

The action of Puregon is similar to that of the natural Follicle Stimulating Hormone (FSH). In the female the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. Puregon can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Puregon can be used to promote multiple follicular developments in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]. Treatment with Puregon is generally followed by administration of hCG to induce the final phase of oocyte maturation including resumption of meiosis, rupture of the follicle to release the oocyte and formation of corpus luteum.

In males deficient in FSH, Puregon should be used concomitantly with HCG for at least four months to promote spermatogenesis.

Puregon powder for solution for injection is presented as a lyophilised cake (75 I.U.) or as lyophilised sphere, a so-called lyosphere (50 I.U., 100 I.U. or 150 I.U.). Each box of Puregon powder for solution for injection contains 1, 3, 5 or 10 ampoules or vials of follitropin (plus 1, 3, 5 or 10 ampoules of solvent for reconstitution containing 1ml of saline solution 0,45%). Puregon can be used for intramuscular or subcutaneous injection. In order to avoid injection of large volumes, 3 to 4 ampoules or vials of Puregon may be dissolved in 1 ml of solvent. When only 1 or 2 ampoules/vials are required, the volume may be reduced to 0.5 ml.

Puregon solution for injection is presented in the following strengths: 50 IU/0.5ml, 75 IU/0.5 ml, 100 IU/0.5 ml, 150 IU/0.5 ml, 200 IU/0.5 ml, 225 IU/0.5 ml and 250 IU/0.5 ml. Each box of Puregon solution for injections contains 1, 5 or 10 vials with solution for intramuscular or subcutaneous injection. There are also two multidose formulations, containing 300 IU/0.36 ml and 600 IU/0.72 ml solutions for injection, filled in cartridge. These presentations are to be used with a pen-injector device. Each box contains 1 cartridges and 7 injection needles.

2. Chemical, pharmaceutical and biological aspects

Puregon consists of a powder for solution for injection containing r-hFSH in a lyophilised form and a solvent for reconstitution. It has high biochemical purity (> 99%) and a high specific biological

activity (approximately 10 000 I.U./mg [1]). Puregon also exists as a solution for injection. For the multidose formulation, benzylalcohol has been added as an anti-microbial agent.

The active substance, follitropin beta, a recombinant human Follicle Stimulating Hormone (FSH) is a glycoprotein. Recombinant human FSH is a heterodimer comprising 2 subunits, namely, an α- and a β- subunit, which are, associated non-convalently. The α-subunit is common to the glycoprotein hormone family consisting of Luteinising Hormone (LH), Thyroid Stimulating Hormone (TSH), and human Chorionic Gonadotrophin (hCG) whereas the specific β-subunit determines the specific biological activity of each hormone.

Follitropin beta is expressed in a Chinese Hamster Ovary (CHO-K1) cell-line used as the host cell system, which has been transfected with two plasmids containing respectively:

- the human FSH α and β genes;
- selector markers.

The Working Cell Bank, obtained from one stable clone producing biologically active human FSH referred to as the Master Cell Bank, undergoes a fermentation process divided into two phases: the pre-production or initiation of a production run and the production phase. The fermentation, which requires defined growth media at 37°C is continuously harvested and filtered aseptically to give a cell-free supernatant containing the recombinant protein. The purification process involves nine separate steps; each designed to remove specific contaminants, leading to the final bulk product for the preparation of the finished product. A batch is defined as the purified half of each harvest from a complete production volume of a 10 litres fermenter. A variation (submitted in July 1996, approved by the Commission in November 1996) increased the batch size of the active substance: the complete harvest or half of each harvest of the complete production volume of the 10 l fermentor can be used for purification.

The characterisation of the active substance revealed that the preparation contains less relatively acidic and more relatively basic isoforms than urine derived FSH.

Post-marketing Activities

In July 1999, the company submitted a type II variation related to the release tests on the active substance (follitropin beta). On basis of the submitted information, the European Commission approved in 22 December 1999 this variation and the new release test/specifications.

Further, the CPMP issued on 28 August 2000 a positive Opinion on a Type II variation concerning changes in test methods and release specifications for the active substance (follitropin beta) of Puregon solution for injection in cartridges. The Commission Decision was amended on 19 January 2001.

The EMEA issued on 22 September 2000 a positive Notification on a Type I variation concerning a change in the in-process control for Puregon solution for injection in vials.

The Company submitted a type II variation on 8 December 2000 to demonstrate compliance with Directive 1999/82/EC and the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. The corresponding Commission Decision was issued on 10 April 2001.

On 12 November 2001, the Company submitted a Type II variation concerning a change of test methods and/or specifications for the active substance. The respective Commission Decision was issued on 19 March 2002.

The EMEA issued on 30 May 2002 a positive Notification on a Type I variation concerning a minor change of manufacturing process of the active substance, which did not require any amendment to the Community Marketing Authorisation.

[1] as determined by the European Pharmacopoeia test for FSH in vivo bioactivity and on the basis of the molar extinction co-efficient at 277 nm (ε_s : mg^{-1} cm^{-1}) = 1.066.

The EMEA issued on 27 June 2002 a positive Notification on a Type I variation concerning a change in the test procedure of the active substance, which did not require any amendment to the Community Marketing Authorisation.

Finished product manufacture for the powder for solution for injection:

The aseptic manufacturing process of the finished product includes two phases, the bulk solution preparation and the preparation of a freeze-dried cake or sphere (lyosphere).

The lyosphere formulation, which is a new lyophilised presentation form of spherical shape, is bioequivalent with that developed for the cake presentation. Cakes are freeze-dried from 0,5 ml bulk solution and lyospheres from 0,1 ml.

The formulated product is contained in a colourless glass ampoule (lyosphere) or glass vial (cake) (Ph. Eur. glass Type 1), sterilised.

Finished product manufacture for the solution for injection:

The excipients are dissolved in water for injections. Follitropin beta in dissolved in the solution. The pH is adjusted to 7.0 if necessary, the solution is diluted to volume with water for injections and the solution is filtered through 0.22 µm membrane filters. The filtered solution is filled aseptically into sterilised vials or cartridges.

The product is presented as an aqueous solution filled in a colourless 3 ml injection vial of hydrolytic resistant glass, type I closed with chlorobutyl rubber closures. The multidose presentation is filled in 1.5 ml cartridges of hydrolytic resistant glass, type I. The cartridges were initially filled with 0.525 ml solution (833 IU/ml) in the 300 IU process and with 0.885 ml in the 600 IU process.

Process validation has been described for at least one batch for each product strength. The specifications for release of the finished product were judged adequate.

The shelf life for the powder for solution for injection is two years when the medicinal product is stored in the containers in which they are supplied, under temperatures below 30 °C, not frozen and protected from light.

For the solution for injection (single-dose and multidose presentations), a 2-year shelf life at 2 °C – 8 °C was initially approved.

Post marketing activities

On 8 December 2000, the European Commission approved a type II variation concerning a change in storage conditions for the Puregon solution for injection (vials and multidose cartridges). The Company provided stability data to justify that the product can be stored below 25°C for a maximum of 3 months. The SPC, labelling and Package Leaflet have been updated accordingly to indicate that the patient may store the product outside the refrigerator.

On 18 October 2001, the European Commission issued a Commission Decision for a type I variation concerning an extension of the shelf life of Puregon solution for injection in vials and Puregon solution for injection in cartridges from 2 years to 3 years. The scope of this variation was to extend the shelf life as foreseen at the time of authorisation. The EMEA notified the European Commission on 13 July 2001 that the variation was accepted.

During the initial assessment procedure of the powder for solution for injection, quality points were raised and resolved by the company:

1. The use of ampoules for lyophilised products, instead of vials has been justified by showing the minimisation of the microbiological risks of contamination.
2. In response to the objections regarding the genetic development of Puregon and the construction of the plasmid, further information was provided.

3. Further data on both Master Cell Bank (MCB) and Working Cell Bank (WCB) have been provided regarding the microbiological quality, the viral control, the genetic and phenotypic stability, and the cell viability. Assurance that fermentation will not exceed 3 months was requested, as characterisation and genetic stability have only been demonstrated for this duration.

4. The company has clarified points with regard to the purification steps and to the quality criteria to justify reprocessing.

Additional information on the pharmaceutical dossier were provided during a hearing held on 13-14 November at the CPMP Working Party Biotechnology/Pharmacy (BWP) on the issues listed below:

1. Validation data on the ISOQUANT method used to study the deamidation of asparagine.

2. Evidence supporting consistency of the carbohydrate analysis particularly in relation to the sialic acid content.

3. Data on the development of a vial to replace the ampoule presentation.

The BWP considered the responses satisfactory but recommended that the company should provide, before a positive opinion is granted, at least 2 pilot scale batches analysis data for each strength and each formulation generated at the Irish manufacturing facility to reassure batch-to-batch consistency.

Few quality points were identified for which additional information has to be provided on an ongoing basis. The company, after having being consulted, committed to provide this information in the timeframe agreed with the CPMP.

During the assessment procedure of the multidose solution for injection, the BWP was asked for their position on the acceptability of a multidose presentation. The BWP accepted that the Company have provided assurance that the risk of microbial contamination has been minimised, although, as with all multi-dose presentations, not eliminated. The company, during an oral explanation at the September 1999 CPMP meeting, provided further assurance on this issue.

3. Toxico-pharmacological aspects

In the framework of non-clinical safety and efficacy testing, Puregon was compared to two widely used commercial preparations: a urine-derived extract with FSH activity virtually devoid of LH activity and a urinary extract with FSH and LH activities.

Pharmacodynamics

The biological properties of Puregon have been compared to reference substances (urinary human FSH and pituitary human FSH) in a series of in vitro and in vivo studies. The receptor binding affinity of follitropin was 2-3 fold higher than that of the urinary or pituitary FSH reference preparations when determined on the basis of their declared in vivo bioactivity (the rat ovarian weight augmentation assay). With regard to the isohormone profile, which is considered to be important in predicting the biological characteristics of the various FSH preparations, Puregon was compared to a urinary FSH preparation using the chromatofocusing technique (pH range 3-6). Similarity in the in vitro and in vivo bioactivity of the 2 preparations was concluded from comparable results obtained for both preparations. However, the isohormone distribution indicated that Puregon contains a two-fold lower proportion of relatively acidic and a two-fold higher proportion of relatively basic isohormones. No potential drug interactions were explored.

Pharmacokinetics

The isohormone composition of FSH preparations, i.e. the proportion of relatively acidic or basic isoforms, influences their kinetic behaviour, and, therefore, their in vivo bioactivities. The company stated that the effects of a change in the isohormone composition of follitropin beta should not represent problems in administering the correct dose, since the doses are adjusted according to individual patient need.

The pharmacokinetic profile was assessed in rats and dogs and included distribution and elimination studies. Both in dogs and in man, the rate and extent of absorption did not differ for intramuscular and subcutaneous administration.

Toxicology

The package of toxicity studies provided includes 2 single dose intramuscular toxicity studies, repeat dose intramuscular toxicity studies (2-4 weeks), and mutagenicity (Ames test) and local tolerance investigations.

Observed toxicity of Puregon was almost entirely related to the pharmacological activity of follitropin beta.

Questions were raised during the assessment procedure and resolved by the company by providing additional data:

1. To assess the toxicological profile of the product after repeated intramuscular administration and to examine the induction of antibodies against r-hFSH, a 13-week study was performed in female and male Beagle dogs, at levels up to approximately 10 times the maximum daily human dose. No overt signs of toxicity were observed. In most animals, Puregon induced the formation of anti-r-hFSH antibodies. An in vivo neutralising effect of these antibodies seems however unlikely because similar exaggerated ovarian stimulation was found in all female animals at all dose levels tested.
2. The absence of reproduction toxicity studies in male animals was justified because these studies are considered not to be relevant for the proposed female indications.
3. The use of only one or two dose groups in many toxicity studies is justified by the absence of intrinsic toxicity of Puregon, therefore the exposure to low doses was not considered to be relevant.
4. Adequate explanation of the choice of intramuscular route in the toxicity studies, whereas the administration route in man is also subcutaneous was submitted by the applicant.
5. An in vitro cytogenetic assay in human peripheral lymphocytes, which revealed no clastogenic activity, was also provided.

4. Clinical aspects

Table 1: Overview of pharmacodynamic studies

Study	Type of study	Study Design	Number of patients	Criteria for inclusion	Dosage regimen	Criteria for evaluation
37601	Tolerance, safety, kinetics and dynamics after single IM dose (Metrodin-compared)	Open group comparative four centre single dose	8 women, 7 men	Gondotropin deficient volunteers in good health	Puregon or Metrodin 300 IU ; IM	Standard safety and dynamics parameters and immunoreactive and bioactive FSH + LH serum concentrations and anti-FSH AB
37602	Tolerance, safety, kinetics, and dynamics after multiple rising IM dose	Open, four centre multiple rising dose	7 women, 9 men	Gondotropin deficient volunteers in good health	Puregon 75Iu, 150 IU, 225 IU ; IM	Standard safety and dynamics parameters and immunoreactive FSH serum concentrations and anti-FSH AB

Table 2: overview of the pharmacokinetic studies

Study	Type of study	Study Design	Number of patients	Criteria for inclusion	Dosage regimen	Criteria for evaluation
37605	Kinetics after single IV, IM and SC dose (Decapeptyl suppression)	Randomised open single centre, single dose, 3 way cross over	18 women	Healthy women with normal cycle	Puregon 300 IU (D15, d29, D43) ; IV, IM, SC	Standard safety parameters, serum LH + FSH immuno-reactivity, Cmax, tmax, AUC(0-132), antiFSH AB
37607	Kinetics after multiple IM administration (Metrodin-compared, Lyndiol suppression)	Randomised single centre group comparative multiple dose	36 women	Healthy women with normal cycle using oral contraception for a least 3 months	Puregon 75 IU, 150 IU, 225 IU; IM	Standard safety and dynamic parameters, follicular growth, E2 and serum FSH immunoreactivity
37614	Kinetics after single IV, SC and IM dose (Lyndiol suppression)	Randomised open single centre, single dose, 3-way cross-over	15 women	Healthy women with normal cycle, using Lyndiol during study	300 IU (D15; D29, D43); IV, IM or SC	Standard safety parameters, serum LH and FSH immuno-reactivity, Cmax, tmax, AUC (0-132) and antiFSH AB
37624	Kinetics after SC administration in multiple-dose regimen, dose proportionality, comparison of kinetics after IM and SC administration	Randomised open, group-comparative, multidose study	48 women (12 in each group)	Healthy female volunteers with normal cycle using oral contraception for a least 3 months	SC : 75 IU, 150 IU or 225 IU for 7 days IM : 150 IU for 7 days	Pharmacokinetics (serum immunoreactive FSH and derived parameters); Pharmacodynamics (follicular number/size, serum oestradiol, serum LH) ; Safety (incidence and nature of AE, pre/post study laboratory and physical examination)

Table 3: overview of the efficacy and safety trials

Study	Type of study	Study Design	Number of patients	Criteria for inclusion	Dosage regimen	Criteria for evaluation
37603	Efficacy and safety in IVF with various pituitary suppression regimens	Open single centre pilot efficacy	51 women	Healthy women of infertile coup-les eligible for IVF	IM	Standard safety parameters, immuno-globulins, anti FSH AB, Finding re: pregnancy, follow-up, delivery, neonatal outcome and children follow-up

37604	Efficacy and safety in IVF without pituitary suppression (Humagon-compared)	Randomised, assessor-blind group-comparative single centre IVF/ET	54 women (Puregon) 35 women (Humegon)	Infertile women in good health, infertility potentially solvable by IVF	150 IU-225 IU (D1 to D4), thereafter dose adjusted per subject; IM	Standard safety, dynamics and efficacy parameters and antiFSH and anti-CHO-cell derived protein ABs
37608	Efficacy and safety in IVF (Metrodin-compared, buserelin suppression)	Randomised, assessor-blind, group comparative multi-centre IVF/ET	1st cycle: 585 women (396 on comparator) 2nd cycle: 206 women (156 on comparator) 3rd cycle: 83 women (56 on comparator)	Infertile women in good health, infertility potentially solvable by IVF	150 IU-225 IU (D1 to D4), thereafter dose adjusted per subject; IM	Standard safety, dynamics and efficacy parameters and antiFSH and anti-CHO-cell derived protein Abs. Finding re: pregnancy, follow-up, delivery, neonatal outcome and children follow-up
37609	Efficacy and safety in Ovulation Induction (Metrodin-compared)	Randomised, assessor-blind, group-comparative multicentre ovulation induction	105 women (Puregon) 37 women (Metrodin)	Infertile women in good health but with chronic anovulation	75 – 225 IU ; IM	Standard safety, dynamic and efficacy parameters and anti-FSH antibodies.
37611	Efficacy and safety in IVF (Metrodin-compared, triptorelin suppression)	Randomised, assessor-blind, group-comparative multicentre IVF/ET	57 women (Puregon) 33 women (Metrodin)	Infertile women in good health, infertility potentially solvable by IVF	150 IU-225 IU (D1 to D4), thereafter dose adjusted per subject; IM	Standard safety, dynamics and efficacy parameters and antiFSH and anti-CHO-cell derived protein Abs.
37612	Efficacy and safety in Hypogonadal men (Humegon-compared)	Randomised, double-blind, group comparative multientre study in hypopituitary men	4 men (Puregon) 2 man (Humegon)	Hypopituitary men in good health with infertility characteristics solvable by FSH-treatment	150 IU at Mon-Wed-Fri ; IM	Sperm characteristics, standard safety parameters
37613	Efficacy and safety in IVF (IM vs SC administration, buserelin suppression)	Randomised, assessor-blind, group comparative multi-centre IVF/ET	77 women (IM) 118 women (SC)	Infertile women in good health, infertility potentially solvable by IVF	150 IU-225 IU (D1 to D4), thereafter dose adjusted per subject ; IM, SC	Standard safety, dynamics and efficacy parameters and antiFSH Abs. Special attention to local tolerance at the injection site.

37616	Efficacy and safety in Ovulation induction (IM vs SC administration)	Randomised open group comparative multicentre ovulation induction	2 women (IM) 2 women (SC)	Infertile women in good health with clomiphene resistant anovulation	Dose depending on body-mass index; IM, SC	Standard safety parameters with special attention to local tolerance at the injection site.
37617	Efficacy and safety in IVF (Puregon IM vs SC vs Humegon IM, buserelin suppression)	Randomised open group comparative single centre IVF/ET	6 women (Puregon, IM) 7 women (Puregon, SC) 7 women (Humegon, IM)	Infertile women in good health infertility potentially solvable by IVF	Fixed dose of 150 IU per day ; IM, SC	Standard safety, dynamics and efficacy parameters, anti-FSH Abs with special attention to local tolerance at the injection site

Introduction

The physiological function of FSH in follicular development is well known. It is claimed that only minor changes exist between the naturally occurring human pituitary FSH and Puregon. These are thought not to affect the receptor binding affinity or the intrinsic bioactivity of this recombinant product.

As stated in the SPC, the therapeutic indications are:

In the female:
Puregon is indicated for the treatment of female infertility in the following clinical situations:

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programmes [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

In the male:
Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

Pharmacokinetics/Pharmacodynamics

Six studies have addressed the primary and secondary pharmacodynamics and pharmacokinetics of Puregon (See tables 1 and 2). From these studies Puregon appears to have similar pharmacodynamic activities to the urinary FSH comparator in terms of inducing ovum growth and maturation as judged by ultrasound and laparoscopic harvesting.

Recombinant FSH is biochemically very similar to human pituitary FSH and is distributed, metabolised and excreted in the same way.

In all pharmacokinetic studies, dosing of Puregon and comparator products was based on in vivo bioactivity, whereas immunoreactive FSH plasma levels were measured for kinetic evaluation.

The pharmacokinetics of a single intramuscular dose or of multiple intramuscular doses were analysed in a pharmacodynamic study versus the urinary FSH comparator. However data were presented on small numbers of patients with large interpatient variability, making interpretation difficult.

After intramuscular or subcutaneous administration of Puregon, maximum plasma concentrations of FSH are reached within 12 hours. Owing to the sustained release from the injection site and the

relatively long elimination half-life of about 40 hours (ranging from 12 to 70 hours), FSH remained increased for 24-48 hours. After single dose administration of Puregon, the absolute bioavailability for the intramuscular and subcutaneous route was approximately 77%. These two routes of administration, although no bioequivalent for T_{max}, were bioequivalent for C_{max} and AUC.

Efficacy data

In clinical conditions with virtually no endogenous FSH and LH activity (i.e. in extremely gonadotropin-deficient women), Puregon induces normal follicular growth, yet estrogen production was severely impaired due to insufficient LH-dependent androgen production.

A full clinical development programme was carried out for studying Puregon (see overview in table 3). The comparator considered as appropriate was a urinary FSH preparation with negligible luteinising activity.

The initial Puregon clinical programme consisted of one large randomised assessor-blind group-comparative study involving 1000 patients (Study 37608 with a Puregon: urinary FSH comparator ratio of 3 : 2). The objective of this study was to evaluate the safety and efficacy of Puregon versus comparator in the induction of controlled ovarian hyperstimulation prior to in vitro fertilisation (IVF)/embryo transfer (ET). The number of oocytes recovered and the ongoing pregnancy rate were defined as main efficacy parameters.

In this study Puregon has been demonstrated to be at least as effective as the comparator. With respect to the other main efficacy parameter, ongoing pregnancy rate, no statistically significant difference between Puregon and comparator groups was found. With inclusion of frozen embryo cycles, Puregon showed a significantly higher pregnancy rate.

It was considered that the indication, controlled ovarian hyperstimulation, was acceptable based on results obtained from this trial.

In relation to the indication of infertility caused by anovulation, the company submitted results obtained from a randomised comparative multicentre safety and efficacy study of Puregon and urinary FSH comparator in women with chronic anovulation (WHO group II- pituitary/ovarian dysfunction yielding a synchronised secretion of both gonadotropin and oestrogen in the presence of normal lactotrophic function) who failed to ovulate and/or to conceive during clomiphene citrate treatment (study 37609).

The primary efficacy parameters for this study were:

- the number of cycles needed to achieve ovulation.
- the cumulative ovulation rate after 3 cycles (using the life-table method).

200 subjects were planned to complete this study. The actual number of subjects recruited into the study was 172. In the Per Protocol (PP) statistical analysis, the number of subjects included was 141, given that protocol violators or patients who could not fully complete the study protocol were excluded.

During the assessment of the application, the company was requested to submit a new analysis restricted to the PP group of subjects who fully completed the study protocol (Restricted Per Protocol RPP involving 122 subjects).

The overall results of this study are presented in table 4.

Table 4- Statistical analysis of the anovulation study:

	INTENT TO TREAT		PER PROTOCOL			
	Report		Report		New (RPP)	
	Puregon	urinary FSH	Puregon	urinary FSH	Puregon	urinary FSH
Cumulative ovulation rate after	(N= 105)	(N= 67)	(N= 86)	(N= 55)	(N= 75)	(N= 47)
Cycle 1	0.72	0.63	0.84	0.80	0.83	0.79
Cycle 2	0.89	0.88	0.96	1.00	0.96	1.00
Cycle 3	0.95	0.96	0.98	1.00	0.98	1.00
Puregon vs Metrodin after cycle 3	- 0.01		- 0.02		- 0.02	
95% Confidence Interval	-0.10 to 0.08		- 0.06 to 0.02		- 0.06 to 0.02	

Considering these results, there are hardly any differences between the two PP analyses. After analysing the impact of the early termination on the power of the study, it was concluded that the differences in ovulation rate after 3 cycles were so small that a reduced sample size did not make a difference.

With regard to these results, which demonstrate the efficacy of Puregon relative to urinary FSH comparator with respect to inducing ovulation in anovulatory women whatever method of analysis used, this indication was considered acceptable.

Questions on efficacy were raised during the assessment and resolved by the company:

1. Efficacy data indicate a stronger potency of Puregon in comparison with urinary FSH, so the recommended dosage schedule may need adaptation.
2. Additional clinical data on the treatment of male infertility were requested. However, the company decided not to pursue this indication.
3. As further clinical data were requested to support the indication “defective follicular ripening and/or corpus luteum insufficiency” the company decided to withdraw this indication.
4. In relation to the requested indication in fertility caused by anovulation, it was considered necessary to state that patients should be unresponsive to clomiphene citrate and to request further data analysis on this study.

Safety profile

During the assessment, in addition to the initial data submitted, further detailed information on safety as well as results on the newborn were requested. The company resolved these two points by providing an updated safety report.

This report on safety data available from 1074 (Puregon) and 498 (urinary FSH comparator) patients who had completed clinical studies with Puregon or urinary FSH (9 clinical efficacy studies and safety studies; 5 studies on the safety, tolerance, pharmacodynamics/pharmacokinetics) was submitted by the company during the assessment procedure.

Most of the reported adverse effects are primarily attributable to the pharmacological properties of the drug, and the character of the treatment. These are related essentially to reproductive system disorders (ovarian hyperstimulation syndrome, ectopic pregnancy, miscarriage, ovarian cyst, vaginal haemorrhage). The other main side effects are related to gastro-intestinal system disorders, mostly abdominal pain.

Table 5: Distribution of adverse effects classified by body system.

		PUREGON (N=1074)		URINARY FSH (N=498)	
Disorders per body system	**Dictionary term (WHO-ART)**	**n**	**%**	**n**	**%**
Reproductive, female	Ovarian hyperstimulation syndrome	53	5.0	20	4.0
	Ectopic pregnancy	23	2.1	17	3.4
Foetal	Miscarriage	33	3.1	21	4.2
Gastro-intestinal system	Abdominal pain	22	2.0	12	2.4

In the light of these results, it seemed that the overall incidence of ovarian hyperstimulation syndrome observed was slightly higher in the Puregon group. However in those studies that allowed statistical analysis, including the IVF and ovulation induction studies, this difference was not significant. The Puregon and comparator groups behaved similarly with respect to the total number of serious adverse effects reported.

In none of the Puregon-treated subjects analysed (treated for either one, two, or three cycles) evidence was found for the induction of specific antibodies, neither anti-FSH nor anti-CHO cell-derived protein antibodies.

With regard to the subcutaneous route, further data were provided to support the evidence of the local tolerance for this route. The applicant submitted further post-marketing safety data with regard to this route of administration. This information supported the local tolerance of the subcutaneous route.

Questions on the Summary of Product Characteristics (SPC) were raised during the assessment procedure. To reflect the data submitted and to address comments by CPMP Members, amendments to the SPC were requested and performed.

Post authorisation activities

Since the approval of the original Marketing Authorisation a number of variations have been authorised which amend the clinical parts of the Summary of Product Characteristics and relevant parts of the Package leaflet.

On 5 October 1998, the European Commission approved a variation to amend the SPC and PL to give additional guidance in order to avoid injection of large volumes and to reduce pain at injection site.

On 21 February 2000, the European Commission approved a variation to amend the dosing advice in point 4.2 of the SPC. In the initial Product Information, it was stated that Puregon is more efficacious than urinary FSH and therefore may require a lower dose. However, the actual dosing advice was based on the dosages used for urinary FSH. The following changes to the product information have been approved in this variation:

- Recommended starting dose of 50 IU (instead of 75 IU) FSH activity in the indication 'Anovulation'.
- Recommended starting dose of 100 IU (instead of 150 IU) FSH activity in the indication 'Controlled ovarian hyperstimulation in medically assisted reproduction programmes'.

Clinical trials and published data have been provided to support this lower starting dose for both indications.

During an oral explanation before the CPMP (September 1999), the company provided their justification for a lower starting dose for both indications. At the September 1999 meeting, the CPMP approved the variation lowering the starting dose for Puregon in the approved indications.

Two extensions of the marketing authorisation have also been authorised by the Commission (26 April 1999 and 23 September 1999, respectively) for additional strengths/pharmaceutical forms (single dose and multiple dose solution for injection). The report of study 37624 (see table 2) has been submitted,

confirming dose proportionality with the existing formulation (powder for solution for injection). The report of study 37626 (An open label, single-dose, cross-over study to study the pharmacokinetics of FSH after administration of two pharmaceutical formulations of Org 32489 in healthy female subjects whose pituitary function has been suppressed by Lyndiol) demonstrates the bioequivalence of the pen-injector solution and the powder for solution for injection. However, this study shows that a higher dose is delivered using the pen injector than when using a conventional syringe. A statement has been included in the SPC of the multidose presentations to reflect this higher delivery with the pen-injector. At the September 1999 CPMP meeting, the company justified the rationale/clinical necessity for the multidose presentation (cartridge) and provided further reassurance on the quality of the multidose presentation with respect to reducing the risk on in-use microbial contamination.

On 8 December 2000, the European Commission approved a type II variation related to a number of changes to the SPC and PL for Puregon.

The main change entails the addition of an extra precaution to the SPC (section 4.4) and PL (section 2) in order to highlight that women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m^2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotropins, even without concurrent OHSS. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

As supporting evidence of the proposed change, the Company provided a review article, a selection of haemostatic studies and case-reports and a line listing of three reports of thrombosis in association with Puregon therapy. The references submitted demonstrate that arterial and venous thrombo-embolism in a variety of sites is a significant problem in association with the use of gonadotropins in assisted reproduction. Also, based on 3 case-reports of thrombo-embolism associated with Puregon, an additional statement has been added in Section 4.8 (Undesirable Effects) of the SPC.

Secondly, in section 4.2 of the SPC, the sentence on possible interaction of Puregon and GnRH agonists has been adapted to reflect the recent approval of GnRH antagonists for the indication "prevention of premature LH rises". The amended text reflects the requirement for an increased total dose of Puregon when using a GnRH agonist as compared to a GnRH antagonist to achieve an adequate follicular response.

Thirdly, in the SPC for the powder and solvent for solution for injection, a warning on possible hypersensitivity and a statement on antibody formation (in sections 4.4 and 4.8, respectively) have been deleted. This was done to bring the text for the powder and solvent for solution for injection, in line with the recently approved text for the solution for injection.

Extension of indication: Treatment of males with deficient spermatogenesis due to hypogonadotropic hypogonadism

On 10 April 2001, the European Commission approved a type II variation concerning the addition of a new indication for Puregon (all strengths and presentations), namely treatment of male subjects who suffer from deficient spermatogenesis due to hypogonadotropic hypogonadism. As a consequence of the new indication, several sections of the SPC and PL were amended.
In addition, the instructions for 'intramuscular administration' in the PL for the 'Powder and solvent for solution for injection' presentations, were changed in accordance with the instructions in the approved PL for the 'Solution for injection' presentations.

Toxico-pharmacological aspects

No new toxico-pharmacological studies were submitted in support of the male indication. Puregon has been tested at levels of up to 50 IU·kg^{-1} in the rat and dog for 4 and 13 weeks, respectively. In addition, levels of up to 500 IU·kg^{-1} have been tested in the rat for up to 2 weeks. No mortalities or toxic effects were observed. Antibody formation was observed in both species, as would be expected.

In the dog, increase in testicular size and reductions in the adrenal gland weight and prostate gland size were observed in response to the expected pharmacological action of the product.
No long-term toxicity or carcinogenicity studies have been performed, as the formation of neutralising antibodies precludes sustained exposure.
Puregon showed no mutagenic potential in a battery of genotoxicity tests.

Intramuscular injection of Puregon for up to 13 weeks in the dog only resulted in findings consistent with the known pharmacology of the product. Longer-term treatment in animals was considered to be impractical due to the formation of neutralising antibodies. The main difference between the use in man and in woman is that female use is over a 2 to 3 week period, repeated up to several times. Men will receive Puregon 3 times a week for up to a maximum of 18 months or longer. However, there is no reason to suppose that long-term use of Puregon in man should be any less safe than the use of the other licensed (recombinant) FSH.

Pharmacodynamics
Puregon, as other FSH preparations, acts by stimulating Sertoli cells, which are active in spermatogenesis. In a rising dose study in which 9 gonadotrophin deficient but otherwise healthy males received weekly rising doses of 75, 150 and 225 IU of Puregon, median serum inhibin concentrations (a marker of Sertoli cell activity) increased from 165U/L at baseline to 466U/L at maximum. LH concentrations remained very low throughout treatment.

Pharmacokinetics
With reference to pharmacokinetics, there is a great deal of interindividual variability. In addition, there is a statistically significant difference between males and females for C_{max} and t_{max} and between Puregon and Metrodin (urine derived FSH) for C_{max} and AUC $_{0\text{-}00}$.
The difference between males and females is thought to be related to subcutaneous fat thickness, leading to a slower drug absorption in females.
Multiple dose studies indicated an accumulation factor of 1.5 to 2.5 over single dose AUCs.

Efficacy
The effective use of FSH for the treatment of deficient spermatogenesis in hypogonadotrophic hypogonadism is proven and there is already a preparation of recombinant FSH licensed in this indication.
The Company has submitted one completed phase III study in support of the indication. This was an open, multicentre, multinational, parallel group, 2-dose regimen (150 IU Puregon sc thrice weekly and 225 IU Puregon sc twice weekly) efficacy and safety study in hypogonadotrophic hypogonadal males aged between 18 and 60.

The primary efficacy parameter was the percentage of men in whom treatment was successful. Treatment was judged successful if the mean sperm concentration of the last two non-missing treatment assessments for that subject was more than 1 million/ml, irrespective of the duration of treatment. The overall success rate was 43%; the success rate by treatment received was 40% for the thrice weekly and 47% for twice weekly groups respectively. Ten men (5 in each group) remained completely azoospermic throughout the treatment period.

Safety
Overall, the incidence of AEs was 80% in the thrice weekly and 60% in the twice-weekly groups. This was an increase from 34% as compared with the frequency of AEs during pretreatment with Pregnyl .
The AEs were scattered throughout the body systems. Six patients experienced AEs during the treatment period, which were thought to be due to the study drug. Among these were two cases of acne, injection site reaction, injection site pain and single cases of varicose veins, gynaecomastia and a dermoid cyst. Distribution of AEs was similar between the two groups.
There were no serious adverse events occurring in the treatment period that were considered related to the treatment drug. There were no deaths.

Renewal of the Marketing Authorisation

The CPMP issued on 29 March 2001 a positive Opinion on an application for a renewal of the Marketing Authorisation for Puregon. The Commission Decision was amended on 26 July 2001.

Postmarketing clinical safety evaluated as part of the renewal procedure

In the 34 clinical trials completed at the time of the application for the renewal of the MA, approximately 4,400 patients were exposed to Puregon. Additionally, sales worldwide during the reviewed period amounted to about 1,415.900 IU. This would equate to an overall maximum of 1,474,900-ovulation induction treatment cycles or 662,400 IVF treatment cycles. This post-marketing review of the clinical safety covers the 4 $^{1}/_{2}$ year period from May 1996-November 2000 and comprised a total of 6 PSURs. No new safety issues were identified in PSURs 1-4 and no SPC changes were made in this regard.

The cumulative 4 ½ year PSUR contained 138 spontaneous reports detailing 193 serious ADRs. There were 65 serious ADRs (61 OHSS, 2 abdominal pain and 2 ovarian disorder) arising from clinical trials. There was a single spontaneous report of a fatal reaction (sudden death unexplained at autopsy) nine days after finishing Puregon treatment. There were two reports of malignant melanoma, both in women with a previous history of skin lesion excision. There were exceedingly few spontaneous reports of adverse pregnancy outcomes.

Although women undergoing ART are generally very healthy, adverse reactions are to be expected. The extremely low reporting rate may be attributable to incorrect prescriber perceptions of adverse event reporting requirements (most ADRs are probably either well-known reactions or common adverse pregnancy outcomes). Ectopic pregnancy or miscarriage/perinatal death arising from clinical trials was not reported as part of these safety reports, since they were considered unrelated to the study drug by the MAH.

During the recent marketing authorisation renewal procedure for another recombinant follitropin, CPMP requested the addition, clarification or relocation of several non product-specific SPC warnings, which were subsequently submitted as part of a variation application. For consistency the MAH was therefore requested during the renewal of Puregon to implement the same SPC warnings as part of a future variation application.

On 5 February 2002, the European Commission approved a type II variation related to a number of changes to the SPC and PL for Puregon. These changes were proposed by the CPMP during the renewal procedure and the MAH had made a commitment to submit the variation.

In section 4.4 (Specific warnings and precautions for use), the warning regarding an increased risk of multiple gestation was supplemented with a statement highlighting that appropriate FSH dose adjustment(s) should prevent multiple follicle development and that multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes.Moreover, the parents should be advised of the potential risks of multiple births before starting treatment.

There have been only two reports of foetal disorder associated with Puregon (one case each of spina bifida and of bilateral iris coloboma). This is possibly an underestimate, as the background incidence in the general population is likely to be increased due to the relatively advanced age of assisted reproduction patients. A warning was therefore considered necessary. For consistency, the following wording already agreed by the CPMP for another recombinant follitropin was added to section 4.4: "the incidence of congenital malformations after Assisted Reproductive technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g maternal age, sperm characteristics) and multiple gestations."

In section 4.4, a general statement concerning reproductive neoplasms was added, since there have been reports of ovarian, breast and uterine neoplasms in women who have received drugs for ovulation induction, including gonadotrophins. The risk of these types of cancer in women who have received

recombinant FSH such as Puregon is unknown. For consistency, the following wording already agreed by the CPMP for another follitropin was added to section 4.4: "There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women".

In section 4.6 (Pregnancy and lactation), an additional text was added in order to provide limited information in the case of inadvertent exposure during pregnancy. For consistency, the following wording already agreed by the CPMP for another recombinant follitropin was added: "there is no indication to use Puregon during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with urinary gonadotrophins. In case of exposure of during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. No teratogenic effect has been observed in animals studies."

On 28 October 2002, the European Commission approved a Type II variation concerning an update of section 4.4 of SPC and section 2 of the PL as requested by the CPMP following the assessment of a pharmaceutical Follow-up Measure related to the manufacturing process. Information regarding the possibility of Puregon to contain traces of streptomycin and/or neomycin that may cause hypersensitivity reactions was included in these sections. In addition, section 4.8 of the SPC and section 4 of the PL were updated to include information regarding the occurrence of rash and erythema based on data from post-marketing experience and assessment of the 6th PSUR.

5. Overall conclusions and benefit/risk assessment

Infertility caused by deficient endogenous production of FSH may be treated by administration of exogenous gonadotropin. Puregon, a biotechnologically prepared medicinal product, can serve as a substitute for natural FSH.

The CPMP has agreed that the application for marketing authorisation contains sufficient clinical data based on a large randomised group-comparative study to support use of Puregon in Assisted Reproductive Technologies in women.

The additional data submitted related to the study evaluating the impact of Puregon in infertility caused by anovulation reassured the CPMP Members about the efficacy of Puregon in that indication.

Based on bioequivalence study, the use of Puregon via the intramuscular and subcutaneous route is supported.After considerable discussion the chemistry, pharmaceutical and biological issues were resolved by the applicant. The batch analysis results obtained from the Irish manufacturing site were in compliance with the specifications. The data submitted demonstrated therefore satisfactory batch-to-batch consistency.

The preclinical studies submitted were judged sufficient to support product safety.Consequently, in the light of all data available, the CPMP issued favourable opinions for different strengths and presentations for granting a marketing authorisation on the following indications:

"In the female:
Puregon is indicated for the treatment of female infertility in the following clinical situations:

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate;
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programmes [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]."

Following the review of additional clinical data submitted by the MAH post-approval *(see above),* the CPMP considered that the use of Puregon with hCG can offer a specific subpopulation of infertile men a chance of fertility. The benefit-risk should be no different from the other rFSH licensed for this indication and there is certainly no indication of any difference based on the limited safety data available from the pivotal study undertaken in support of the male indication. There is, of course, a

substantial body of reassuring safety data from the use of Puregon in women, although in women treatment is over a shorter time period.

Consequently, in the light of all data available, the CPMP issued favourable opinions for the extension of the indication to include also the following clinical situation:

"In the male:
Deficient spermatogenesis due to hypogonadotrophic hypogonadism."

Further, during the period covered by the cumulative safety data provided with the renewal application (May 1996 – November 2000) *(see above),* no major new safety signals have arisen and the CPMP concluded that the benefit/risk for Puregon remains positive.

Benefit/risk assessment

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk profile of Puregon was favourable in the treatment of infertility in women who either have not responded to treatment with another ovulation stimulant (clomiphene citrate) or who are undergoing treatment for assisted reproduction techniques, like in vitro fertilisation and in men with deficient spermatogenesis due to hypogonadotrophic hypogonadism.